A Dissertation on

"A STUDY OF DEXMEDETOMIDINE,TRAMADOL AND PETHIDINE IN THE PREVENTION OF INTRAOPERATIVE SHIVERING IN PATIENTS UNDERGOING SURGERY UNDER SPINAL ANAESTHESIA"

submitted to

THE TAMILNADU DR M.G.R.MEDICAL UNIVERSITY

in partial fulfilment for the award of the degree of

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

BRANCH X

DEPARTMENT OF ANAESTHESIOLOGY

& CRITICAL CARE

STANLEY MEDICAL COLLEGE

CHENNAI-600 001

APRIL 2016

DECLARATION BY THE CANDIDATE

I hereby declare that the dissertation entitled "A STUDY OF DEXMEDETOMIDINE,TRAMADOL AND PETHIDINE IN THE PREVENTION OF INTRAOPERATIVE SHIVERING IN PATIENTS UNDERGOING SURGERY UNDER SPINAL ANAESTHESIA" has been prepared by me under the Guidance of PROF.DR.S.KRISHNA KUMAR, M.D., Professor of Anaesthesiology, Department of Anaesthesiology, Stanley Medical College, Chennai, in partial fulfilment of the regulations for the award of the degree of M.D(ANAESTHESIOLOGY), examination to be held in April 2015.

This study was conducted at Department Of Anaesthesiology, Stanley Medical College, Chennai.

I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Date :

Place : Chennai DR.AZHAGAPPAN.C

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled, "A STUDY OF DEXMEDETOMIDINE,TRAMADOL AND PETHIDINE IN THE PREVENTION OF INTRAOPERATIVE SHIVERING IN PATIENTS UNDERGOING SURGERY UNDER SPINAL ANAESTHESIA" submitted by Dr.AZHAGAPPAN.C, under the guidance of PROF.DR.S.KRISHNA KUMAR in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by The Tamilnadu Dr.M.G.R.Medical university , Chennai is a bonafide record of the work done by him in the DEPARTMENT OF ANAESTHESIOLOGY & CRITICAL CARE, Stanley Medical College, during the academic year 2014-2015.

Prof Dr. S.KRISHNA KUMAR M.D.

Prof and Guide, Department of Anaesthesiology and critical care,

Stanley Medical College,

Chennai-600 001.

CERTIFICATE BY THE HOD

This is to certify that the dissertation entitled, "A STUDY OF DEXMEDETOMIDINE,TRAMADOL AND PETHIDINE IN THE PREVENTION OF INTRAOPERATIVE SHIVERING IN PATIENTS UNDERGOING SURGERY UNDER SPINAL ANAESTHESIA" submitted by Dr.AZHAGAPPAN.C, under the guidance of PROF.DR.S.KRISHNA KUMAR in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by The Tamilnadu Dr.M.G.R. Medical university , Chennai is a bonafide record of the work done by him in the DEPARTMENT OF ANAESTHESIOLOGY & CRITICAL CARE, Stanley Medical College, during the academic year 2014-2015.

DR.N.LATHA.M.D.,D.A.,

Prof and HOD,

Department of Anaesthesiology & critical care,

Stanley Medical College,

Chennai-600 001.

ENDORSEMENT BY THE DEAN

This is to certify that the dissertation entitled,“A study of dexmedetomidine,tramadol and pethidine in the prevention of intraoperative shivering in patients undergoing surgery under Spinal anaesthesia” submitted by Dr.AZHAGAPPAN.C, under the guidance of PROF.DR.S.KRISHNA KUMAR, in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by The Tamilnadu Dr.M.G.R. Medical university, Chennai is a bonafide record of the work done by him in the DEPARTMENT OF ANAESTHESIOLOGY & CRITICAL CARE, Stanley Medical College, during the academic year 2014-2015.

DR.ISAAC CHRISTIAN MOSES. M.D., FICP, FACP

DEAN,

STANLEY MEDICAL COLLEGE,

CHENNAI-600 001.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to **DR.ISAAC CHRISTIAN MOSES. M.D., FICP, FACP.** Dean, Government Stanley Medical College and Hospital for having permitted me to utilize the facilities of the hospital for the conduct of the study.

My heartfelt gratitude to **Prof. Dr. N . LATHA M.D., D.A.,** Professor and Head, Department of Anaesthesiology, Government Stanley Medical College and Hospital for her motivation, valuable suggestions, expert supervision, guidance and for making all necessary arrangements for conducting this study.

I thank **Prof Dr. S. KRISHNA KUMAR M.D.** for his constant motivation and support apart from providing immense help and valuable suggestions in carrying out this study. His continuous support and ideas are the key factors for the construction of the study.

I thank **Prof Dr. S. Ponnambala Namasivayam M.D.,D.A.,D.N.B,** for his constant motivation, guidance and valuable suggestions in carrying out this study.

I thank **Prof. Dr. DHANASEKARAN, M.D., D.A.,** for his constant support and encouragement throughout the study.

I thank **Prof. Dr KUMUDHA LINGARAJ, M.D., D.A.,** Professor, Department of Anaesthesiology**,** Government Stanley Medical College and Hospital for her motivation, constant encouragement and support.

I express my heartfelt gratitude to Assistant Professors **Dr. MAHALAKSHMI M.D, DR. SARAVANA KUMAR M.D** who had evinced constant and keen interest in the progress of my study right from the inception till the very end and was instrumental in the successful completion of the study.

I wish to thank all Assistant Professors especially for their aid and encouragement during the study.

I thank **Mr. VENKATESAN,** for helping me in statistical analysis.

My sincere thanks to all those post graduates who helped me during this study period.

I thank the staff nurses and theatre personnel, Government Stanley Medical Hospital for their cooperation and assistance.

I owe my gratitude to all the patients included in the study and their relatives, for their whole hearted co-operation and consent.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 01

INTRODUCTION

Shivering is a common and distressing experience to many patients which occurs either during or immediately after the surgery. It is defined as an involuntary, repetitive activity of skeletal muscles. The incidence of shivering varies but is very high and the incidence is approximately 40 – 50% [1].

Mammals are homeothermic. They need a nearly constant internal body temperature. Human core temperature normally ranges from 36.5^0C to 37.5^0C. Anterior hypothalamus integrates thermal inputs from different tissues of the body and compares peripheral information with a set point or threshold value. Temperature lower than this set point will result in responses to warm the body while temperatures higher will trigger reflexes to cool the body [2].

In patients undergoing neuraxial anaesthesia, shivering is a normal thermoregulatory mechanism as evidenced by the presence of vasoconstriction before shivering [3]. Spinal anaesthesia impairs the thermoregulatory system by inhibiting vasoconstriction, which plays an important role in temperature regulation [4]. Spinal anaesthesia results in redistribution of core heat to the periphery from the trunk [below the level of block] [5]. Both these effects predispose patients undergoing spinal anaesthesia to hypothermia and shivering.

Studies in recent years have shown that even mild hypothermia (1^0C – 2^0C) can triple the incidence of adverse cardiac outcomes. An increase in surgical blood loss and increase in need for blood transfusion by 20% is also noted. All these factors leads to a prolonged hospitalization.

Shivering during surgery leads to an uncomfortable experience to the patient along with that leads to an increase in oxygen consumption and carbon dioxide production by two to three fold. Shivering can also increase catecholamine production, lactic acidosis, intraocular pressure, intracranial pressure [6]. Mild shivering increases oxygen consumption like that produced by light exercise but severe shivering can increase oxygen consumption and metabolic rate by 100 – 600%. This can prove detrimental to patients with limited cardiac reserve. Shivering also creates difficulty in monitoring the patients as most of the multi parameter monitors used for anaesthesia show erroneous values.

Treatment of shivering consists of both non-pharmacological and pharmacological methods. Non-pharmacological methods of treatment include external heating like use of blankets, forced air warmers and warmed fluids, maintaining operating room temperature etc.,

Pharmacological methods for treatment of hypothermia is the next resort to treat all these patients. A number of drugs were studied and are being used. Most commonly used drugs include meperidine, tramadol,

clonidine, dexmedetomidine, alfentanil, ketanserin, magnesium sulphate, nefopam etc.,

Meperidine/pethidine is the drug which is being used for the prevention and treatment of shivering for many decades. Many studies on tramadol showed its efficacy in the treatment of shivering. Tramadol produces adverse effects like nausea, vomiting, dizziness etc., which can create further discomfort to the patient [7,8]. Dexmedetomidine is a selective α2 adrenergic agonist and has 1600 times greater selectivity for the α2 adrenoceptor compared with the α1 receptor. It produces sedation, anxiolysis, hypnosis, analgesia, sympatholysis and has anti shivering properties [9].

CHAPTER 02

AIM

To evaluate the efficacy of dexmedetomidine, tramadol and pethidine in the prevention of intra operative shivering in surgeries done under spinal anaesthesia.

OBJECTIVES

PRIMARY OBJECTIVE

1. To study the efficacy of dexmedetomidine, tramadol and pethidine in the prevention of intra operative shivering.

SECONDARY OBJECTIVE

1. To assess the level of sedation caused by these drugs.
2. To study the side effects caused by the study drugs.

CHAPTER 03

NORMAL THERMOREGULATION

It is based on multiple signals from all types of tissue. Processing of signals occurs in three phases, namely, 1) afferent thermal sensing, 2) central regulation and 3) efferent responses.

I. Afferent input

Information about temperature sensation is acquired from thermally (warm and cold) sensitive cells all over the body. Cold receptors increase their firing rate when temperature decreases whereas warm receptors do so when temperature increases. The sensors for firing belongs mostly to a class of transient receptor potential (TRP) protein receptors[10].

Warm signals travels via unmyelinated C fibres and cold signals via Aδ nerve fibres but there is a certain degree of overlap [11]. Since C type fibres also carry pain sensation, intense heat appears similar to sharp pain. Thermal signals pass through spinothalamic tracts.

The spinal cord, hypothalamus, other parts of brain , thoracic and deep abdominal tissues, and skin surface contribute about 20% each of total thermal input to the central regulatory system [12].

II. CENTRAL CONTROL

Temperature regulation is done primarily by central structures, namely the hypothalamus which integrates thermal inputs from skin surfaces and deep tissues with thresholds for each thermal response. Preoptic region of anterior hypothalamus is the most important autonomic thermoregulatory centre. Before integration of thermal inputs, "pre processing" of these inputs is done in the spinal cord and other areas of central nervous system. Some thermoregulatory responses can be dealt by spinal cord itself [13].

The way by which the absolute threshold temperature is determined by the body is still unknown, but mechanisms, appear to be mediated by norepinephrine, dopamine, neuropeptides, 5- hydroxy tryptamine.

Thresholds vary based on sex, circadian rhythm, menstrual cycle, infection, food intake, hypothyroidism or hyperthyroidism, exercise, anaesthetic and other drugs like sedatives, alcohol and nicotine etc., Both vasoconstriction and sweating thresholds are 0.3^0C– 0.5^0C lower in men than in woman. Central control is intact even in premature infants. But, thermoregulatory control is slightly impaired in elderly [14].

Control of autonomic responses is 80% determined by thermal signals from core structures [15]. The interthreshold range (core temperatures not triggering autonomic thermoregulatory responses) is only a few tenths of a degree centigrade. It is bounded by sweating threshold at one end and that

of vasoconstriction at the other end. Humans normally maintain core temperatures tightly.

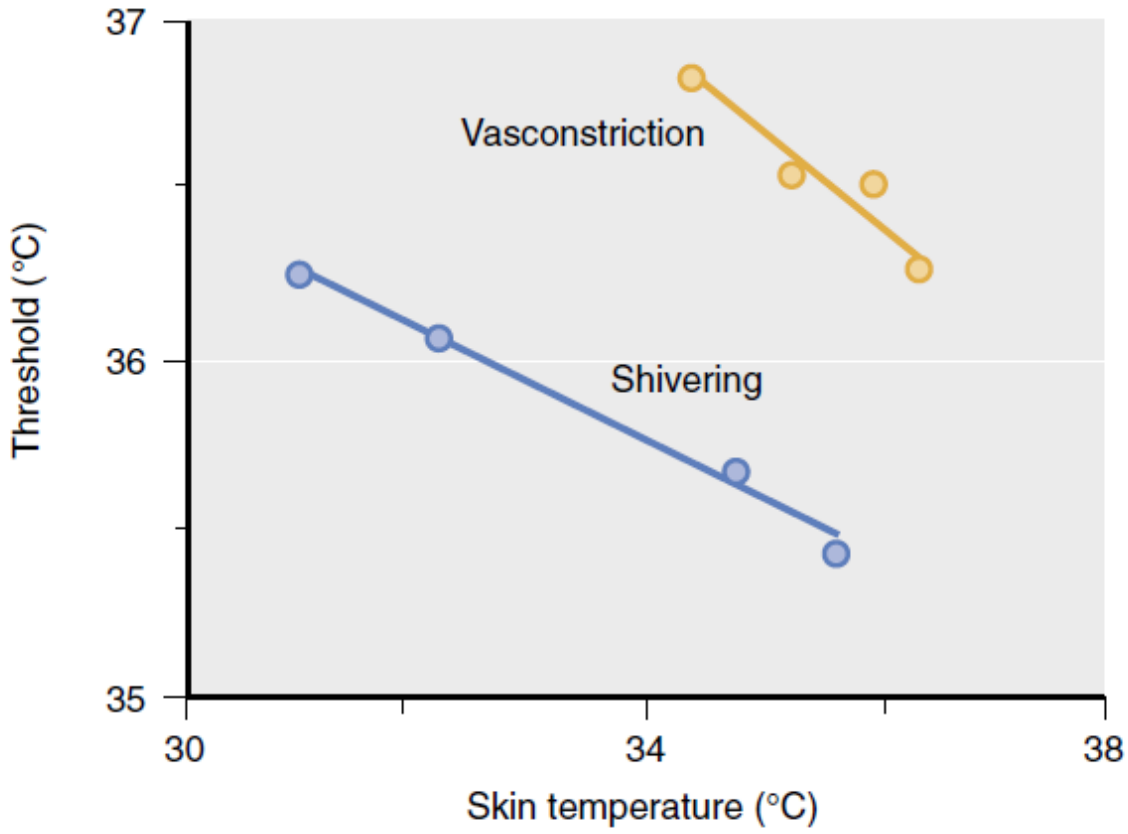


FIGURE 1 : Relationship between mean skin temperature and core temperature triggering vasoconstriction and shivering.

III. EFFERENT RESPONSES

Human body responds to temperature variations by various effector mechanisms which changes heat production or changes environmental heat loss. Each thermal response has its own threshold and gain and so, progresses orderly in response to need.

Energy efficient receptors like vasoconstriction are initiated before metabolically costly responses like shivering occurs. The interthreshold range in humans is 0.2^0 C only.

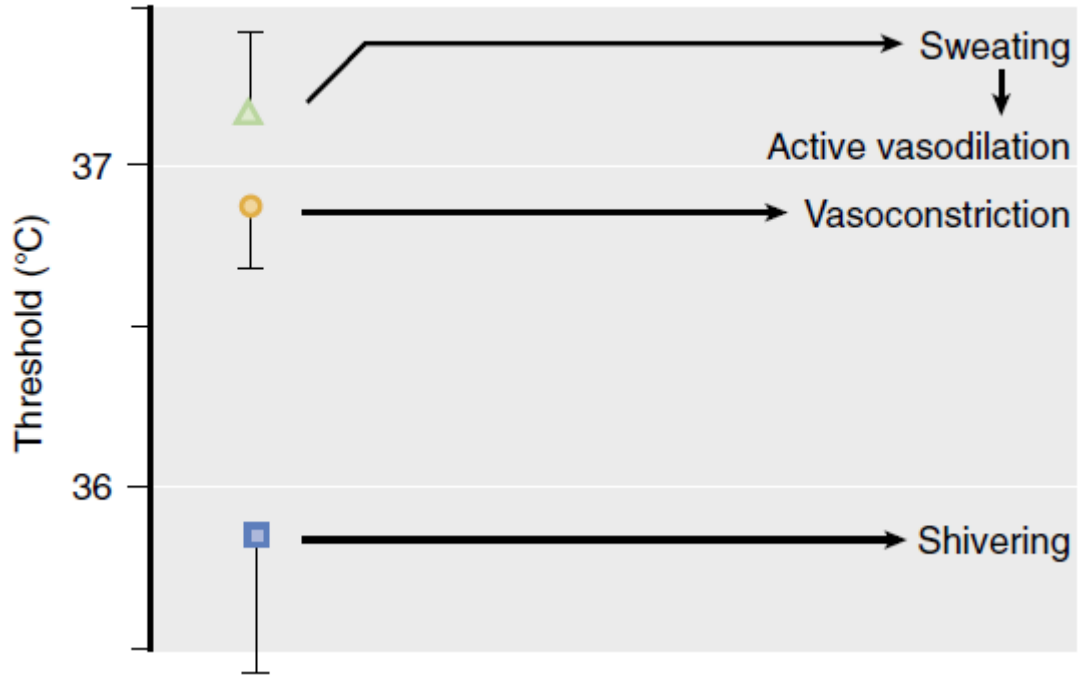


FIGURE 2 : Interthreshold temperature range

The most commonly used effector mechanism is cutaneous vasoconstriction. Vasoconstriction reduces heat loss by convection and radiation. Total digital skin blood flow can be divided into nutritional [mainly capillary] and thermoregulatory [mainly arteriovenous shunt] components [16]. The thermoregulatory arteriovenous shunts vasoconstriction is mediated by local α – adrenergic sympathetic nerves.

Non shivering thermogenesis increases heat production. The major sources in adults are brown fat tissue and skeletal muscle. The metabolic rate is controlled by nor epinephrine in both these tissues.

Behavioural regulation is the most important effector mechanism. It includes modifying environmental temperature, dressing appropriately, voluntary movements and assuming position that oppose skin surface. Behavioural compensation is irrelevant during general anaesthesia as patients are unconscious and mostly paralysed.

On the other end of the spectrum, sweating is produced by postganglionic, cholinergic nerve fibres [17]. Vasodilation is mediated by nitric oxide.

NEURAXIAL ANAESTHESIA AND THERMOREGULATION

Autonomic thermoregulation is impaired during regional anaesthesia and results in intra operative core hypothermia. Spinal and epidural anaesthesia, both reduce the shivering and vasoconstriction thresholds above the level of the block by about 0.6^0C. The shivering and vasoconstriction thresholds are comparably decreased during regional anaesthesia[18] indicating an alteration in central control.

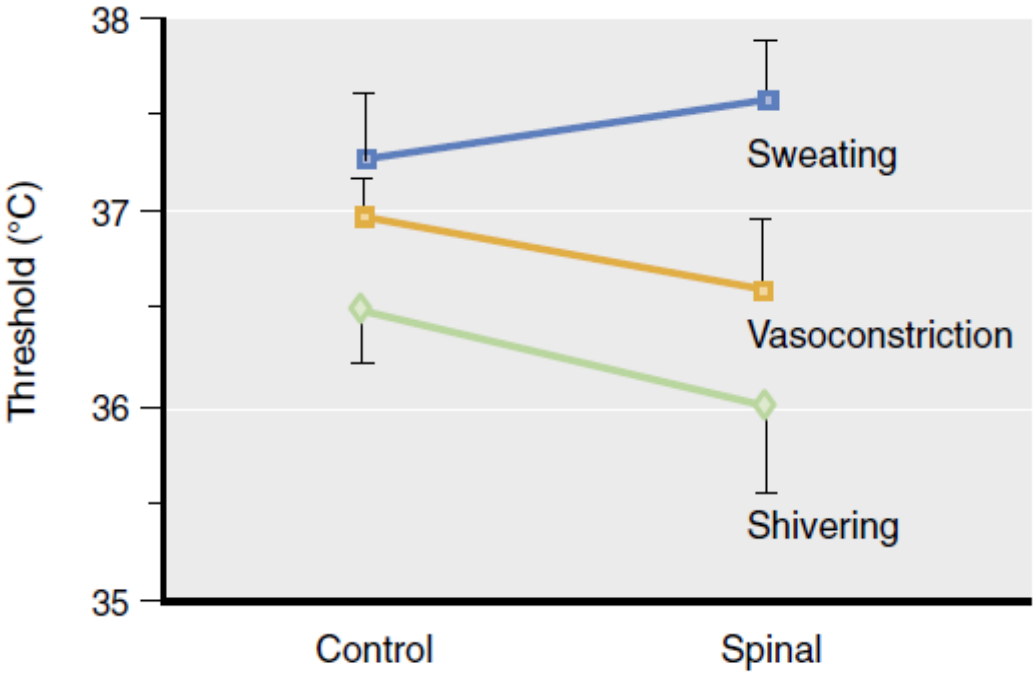


Figure 3 : Spinal anaesthesia increased the sweating threshold but decreased the shivering and vasoconstriction thresholds.

The mechanism involving impairment in centrally mediated thermoregulation via peripheral administration of local anaesthetic involves alteration in afferent thermal inputs from legs. The key factor is that, tonic cold signals dominates thermal input at legs skin temperature in typical operating room conditions. Regional anaesthesia alters the thermal inputs from blocked regions which is primarily cold information. Brain interprets this decreased cold information as relative leg warming.

This is an unconscious process, as perceived temperature does not increase [19]. Since, skin temperature remains an important input to the thermoregulatory system, leg warming proportionately decreases the shivering and vasoconstriction thresholds. What appears to be more

significant is the fact that, the reduction in thresholds is proportional to the number of segments blocked [20].

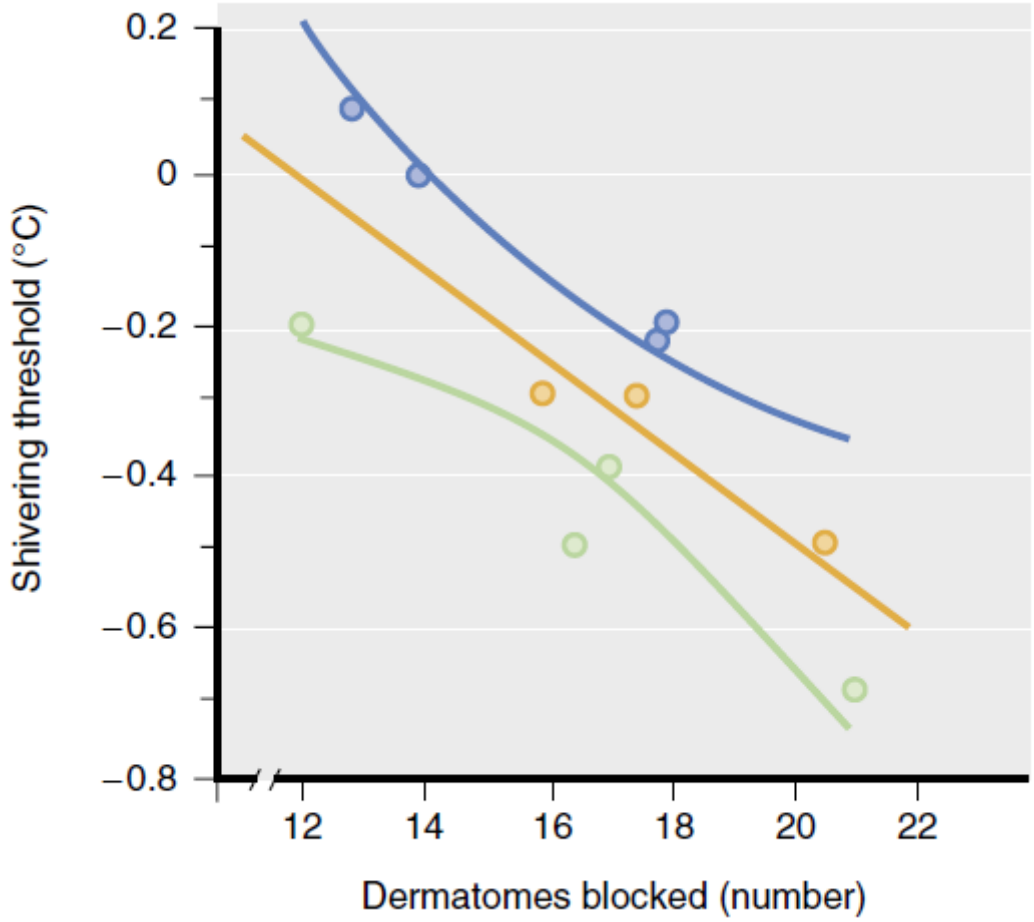


Figure 4 :The number of dermatomes blocked versus shivering threshold. The shivering threshold was decreased by more extensive spinal blocks.

Neuraxial anaesthesia is many a times, supplemented with sedatives which impairs thermoregulatory control [21]. This inhibition becomes severe when associated with other factors like old age, pre-existing illness and also by neuraxial blockade.

Interestingly, patient does not perceive cold during regional anaesthesia. The reason behind this is that, temperature sensation is largely determined by skin temperature and not by core temperature. During regional anaesthesia, decrease in core temperature is associated with an increase in skin temperature. This results in a feeling of increased warmth associated with triggering of autonomic thermoregulatory responses like shivering [4].

Overall, neuraxial anaesthesia inhibits many aspects of thermoregulatory control. Behavioural regulation is impaired. The shivering and vasoconstriction thresholds decreased. All these factors, results in triggering of cold defences at a lower temperature than normal. Patients do not recognize that they are hypothermic too. Defences are less effective even when it is triggered.

Hypothermia during general anaesthesia

Heat may be transferred to the environment from the patient in four ways, namely, conduction, radiation, convection and evaporation. Among these mechanisms, convection and radiation appears to contribute most to perioperative heat loss.

Patterns of intraoperative hypothermia

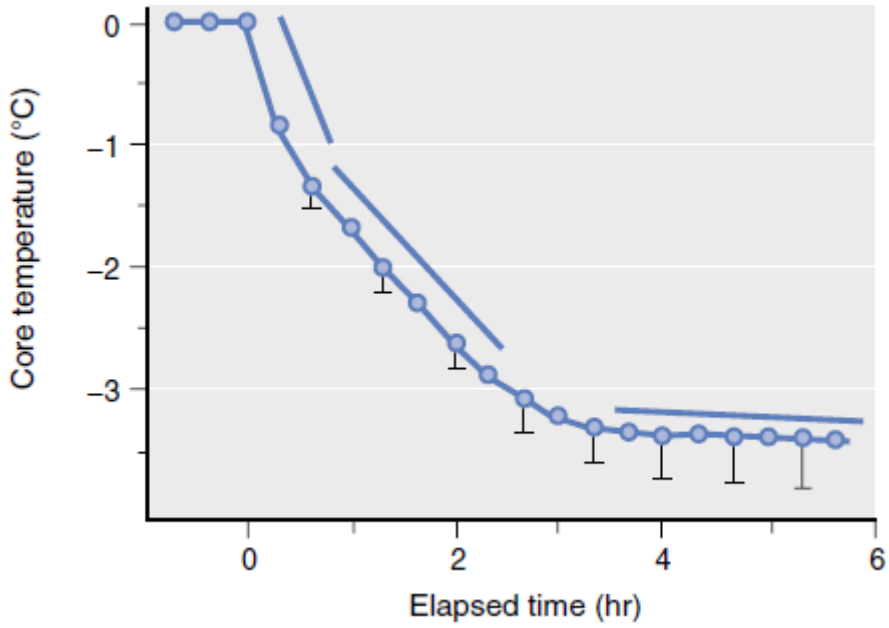


Figure 5 : Patterns of intraoperative hypothermia

core temperature changes characterized by a rapid fall followed by a slow fall and then a plateau phase being reached.

SHIVERING

Shivering is preceded by hypothermia and vasoconstriction. Shivering is an involuntary muscular activity which increases metabolic heat production around 600% above basal level[22]. Shivering can be elicited on cooling the preoptic region of the hypothalamus. Shivering during regional anaesthesia can be treated by warming sentient skin as this augments cutaneous thermal input to central thermoregulatory system and so, increases the degree of core hypothermia tolerated.

Unfortunately, etiology of postanaesthesia shivering like tremors is still unclear. There exists at least two distinct tremor patterns[23]. First is a

tonic pattern similar to normal shivering typically at 4 – 8 cycle/min waxing and waning pattern. Second is a phasic, 5 to 7 Hz bursting pattern like pathologic clonus [24]. Both these tonic and phasic patterns are thermoregulatory responses, characterized by the precedence of core hypothermia and arteriovenous shunt vasoconstriction. Although the precise etiology remains unclear, it may be due to anaesthetic induced disinhibition of descending spinal reflexes.

TEMPERATURE MONITORING

Temperature monitoring should be accurate. Mercury-in-glass thermometers which were used earlier were cumbersome and so, now are replaced by electronic systems. The most commonly used systems are thermistors and thermocouples. Both these devices are accurate and are inexpensive. Infrared monitors used for tympanic membrane temperature monitoring from outer ear are unreliable [25].

Core temperature can be monitored at nasopharynx, distal part of the oesophagus, tympanic membrane, pulmonary artery. The core thermal component contains highly perfused tissues and the temperature here is high when compared with the rest of the body. Core temperature may be measured with accuracy using oral, axillary or rectal temperatures also.

The objective of temperature monitoring is to detect changes in body temperature during anaesthesia.

1. Core temperature to be monitored in patients under general anaesthesia for greater than 30 minutes.
2. Temperature monitoring during regional anaesthesia to be done if adverse changes in temperature expected.
3. Core temperature to be maintained greater than 36^0 C unless hypothermia is indicated.

Prevention of post anaesthesia shivering

Management of shivering does not restrict itself to pharmacotherapy alone, as the heat balance is lost during regional anaesthesia and drugs will still delay the heat recovery. Therefore, shivering must be first of all prevented by offsetting hypothermia.

Maintaining the operating room temperature is a critical step as it determines the heat loss to the surroundings by convection and radiation. Cutaneous heat loss is directly proportional to the body surface area and in small infants, head forms the bulk of body surface area. In adults, head contributes less and exposed arms contribute more and can result in substantial heat loss.

Cutaneous heat loss can be decreased by draping the skin surface with passive insulation like cotton blankets, plastic sheets, surgical drapes, space blankets. Most of the insulators are provided with a layer of air trapped below the covering. A single layer of an insulating material

decreases heat loss by 30%, but including additional layers does not increase the benefit proportionally [26].

Passive insulation alone is insufficient and methods of active skin warming needed. It includes circulating water and forced air warmers. Circulating water mattresses are ineffective if placed below the patient as only small amount of heat is lost between the patient and operating table. It has to be placed over the patient to increase the effectiveness. Forced air warming is the most effective available method[27]. Forced air warmers usually maintain normothermia even during major surgical procedures.

Patients cannot be warmed by giving warm intravenous fluids as fluids cannot be heated above body temperature. On the other hand, administration of 1litre of crystalloid solution or one unit of refrigerated blood will decrease the body temperature by $0.25^{o}C$. Fluid warmers can be used to minimise these losses and may be used when large quantities of fluids are to be administered and contributes little in smaller cases.

Combining all these methods the goal is to maintain the core temperature above $36^{0}C$. Forced air warmer or a combination of forced air warmer and fluid warmer along with proper covering of the patients is needed to maintain normal core temperatures during anaesthesia.

PHARMACOTHERAPY

Nefopam which is used as an analgesic has powerful antishivering properties. Tramadol inhibits reuptake of 5 Hydroxy tryptamine and

norepinephrine. Cerebral α2- adrenoceptors play a role in the inhibition of shivering. Acetylcholine and nicotine prevents shivering. Physostigmine, a cholinesterase inhibitor medication is a potent antishivering agent.

Pure μ agonists like morphine, fentanyl and alfentanyl are used in the treatment of shivering. Epidurally administered sufentanyl produces a dose dependant decrease in shivering. **Pethidine decreases the shivering threshold twice as much as the vasoconstriction threshold**. The antishivering activity of pethidine is also mediated by k opioid receptors. Magnesium sulphate is a physiologically occurring NMDA receptor antagonist and has anti shivering properties. Ketamine is another competitive NMDA receptor antagonist, shown to be effective against shivering. Clonidine and dexmedetomidine are used for the prevention of shivering. Recently, granisetron an antiemetic drug whose role in prevention of shivering is under study. A number of drugs have been studied and still the search for ideal anti shivering agent continues.

Consequences of hypothermia and shivering

1. Reversible coagulopathy (platelet dysfunction)
2. Increased blood loss
3. Increased blood transfusion
4. Impaired wound healing
5. Increased risk of infection

6. Delayed drug metabolism
7. Left shift of haemoglobin – oxygen dissociation curve
8. Altered mental status
9. Cardiac arrhythmias and ischaemia
10. Increased peripheral vascular resistance.
11. Increased myocardial oxygen consumption
12. Increases basal metabolic rate
13. Monitoring artefacts – shows aberrant values.

DEXMEDETOMIDINE

DISTRIBUTION AND PHYSIOLOGICAL RESPONSES MEDIATED THROUGH α_2 . ADRENOCEPTORS

Adrenoceptors are membrane bound receptors that mediate the responses of catecholamines, adrenaline and noradrenaline[28]. In 1948, Ahlquist classified them into two distinct classes: alpha (α) and beta (β)[29]. Alpha adrenoceptors were further divided into α_1 and α_2 based on their anatomical location .The post synaptic α adrenoceptor which mediated responses in the effector organ was designated as α_1 and the presynaptic α adrenoceptor which regulated the release of noradrenaline was designated as α_2[30].α_2 adrenoceptors are widely distributed throughout the CNS and peripheral tissues and they control the modulation of sympathetic nervous system . α_2 adrenoceptors include three highly homologous subtypes α_{2A}, α_{2B}

and α_{2C} , which are required for normal regulation of presynaptic neurotransmitter release from sympathetic nerves in the heart and from the central noradrenergic neurons .

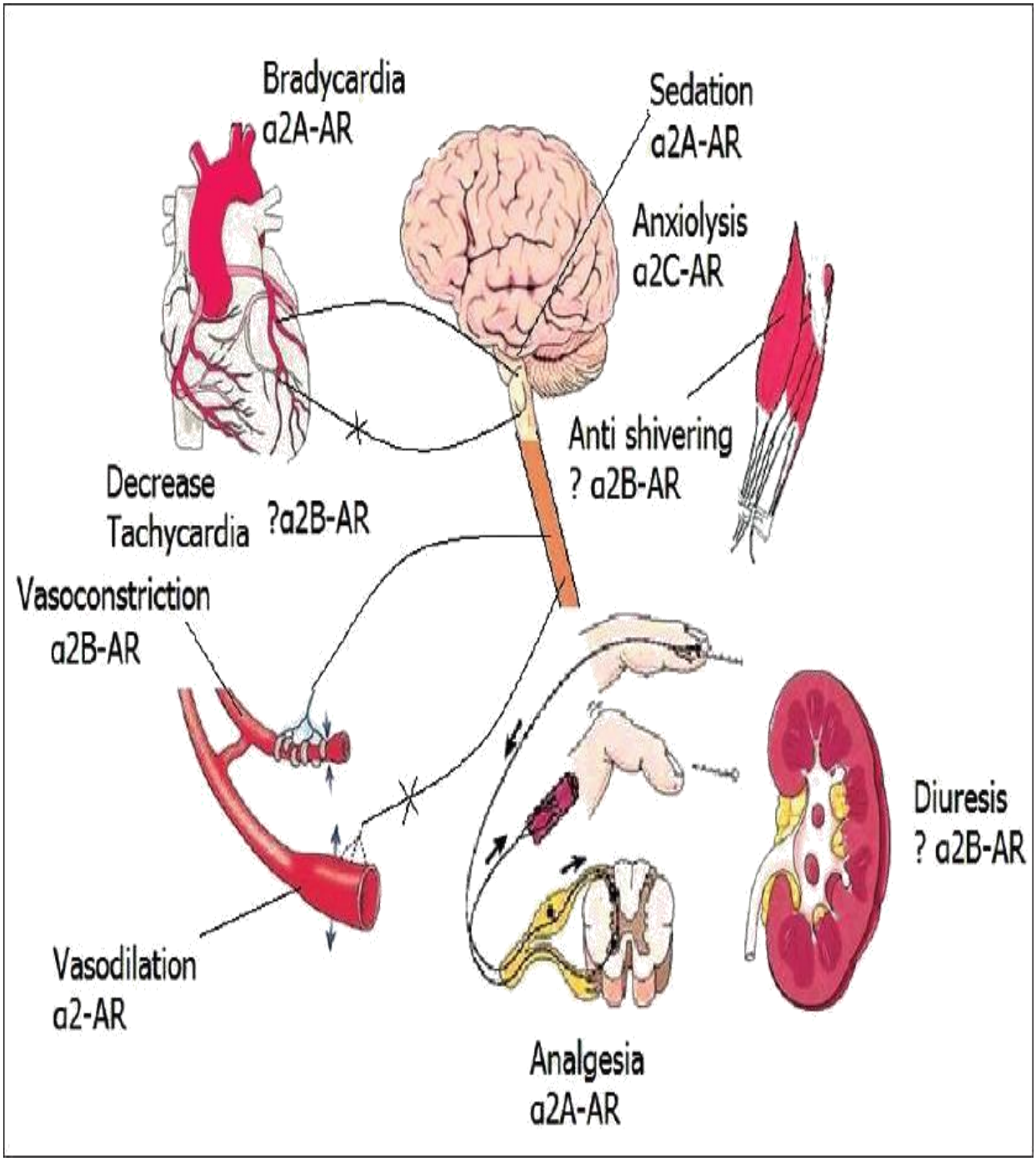


Figure 6: Location and physiological responses mediated through α_2 adrenergic receptors

LOCATIONS AND PHYSIOLOGIC RESPONSES MEDIATED THROUGH α 2 ADRENERGIC RECEPTORS[31]

Location of α2 Receptors	Response mediated through α 2 Receptors
Central nervous System	Inhibition of neurotransmitter release leading to decreased neuronal firing causing bradycardia, hypotension, sedation, sleep and analgesia
Vascular	Smooth muscle contraction by direct action leading to vasoconstriction Vasodilatation due to central sympatholysis Platelet aggregation
Gastrointestinal Tract	Decreases salivation, intestinal secretion and bowel Motility
Pancreas	Decreases insulin release
Hypothalamus	Increases growth hormone release
Adipose tissue	Inhibits lipolysis
Kidney	Inhibits renin release Increases glomerular filtration Increases secretion of Na+ and H20
Eye	Decreases intraocular pressure

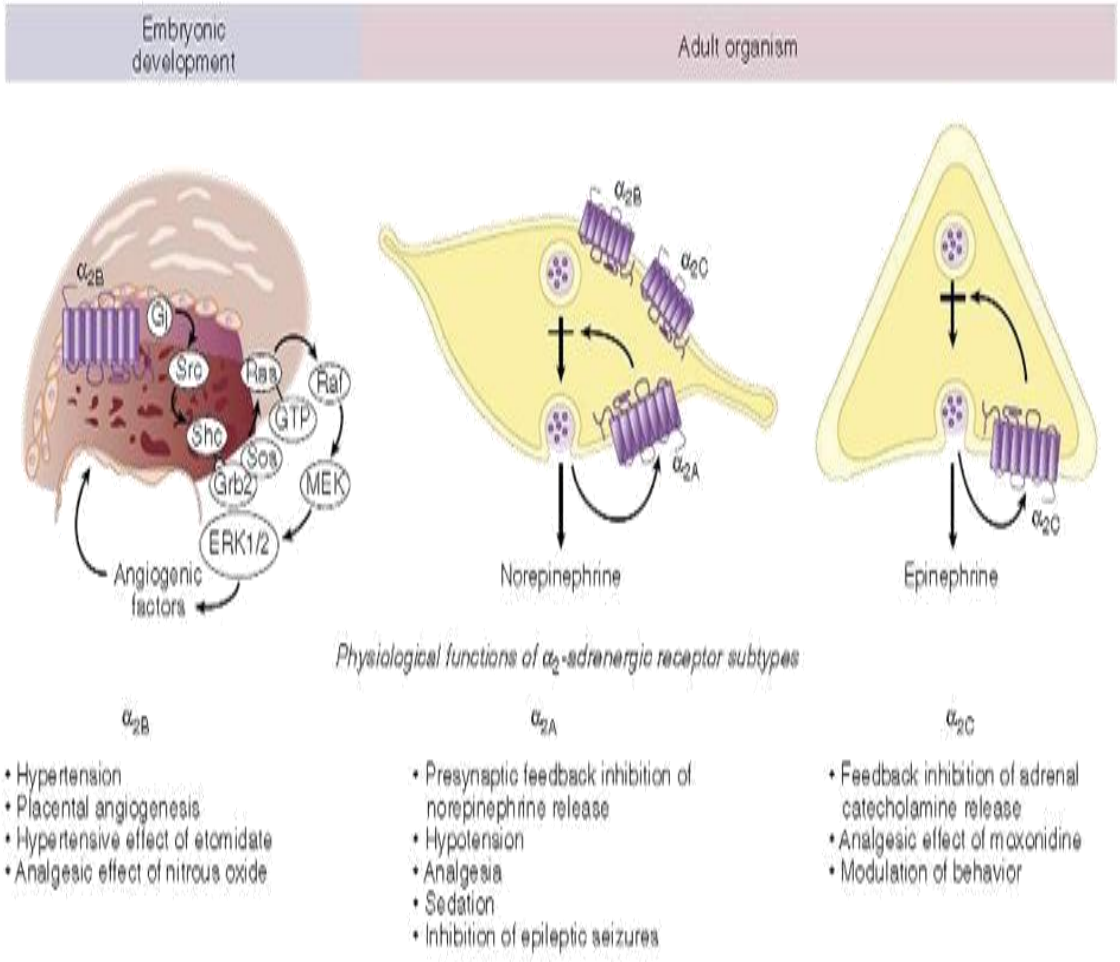


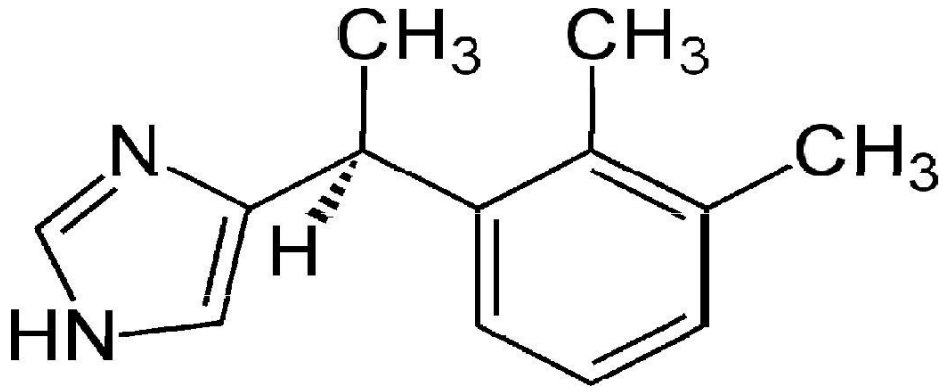
FIGURE 7: Physiologic functions of α2 adrenergic receptor

The *top panel* depicts the three α2 receptor subtypes acting as presynaptic inhibitory feedback receptors to control the release of norepinephrine and epinephrine from peripheral or central adult neurons. Also, a negative feedback loop has been seen in the adrenal gland. Alpha2B receptors have been involved in the development of the placental vascular system during prenatal development. The *lower panel* lists a series of physiologic effects with its associated α2 adrenoreceptors.

DEXMEDETOMIDINE

Dexmedetomidine is an α_2 adrenergic agonist. It produces sedation, anxiolysis, hypnosis, analgesia, sympatholysis and has anti shivering properties. Dexmedetomidine is a highly selective agonist at α2 receptor with 1600 times greater selectivity for the α_2 receptor compared with the α_1 receptor.

Dexmedetomidine is a d-enantiomer of medetomidine, belonging to the imidazole subclass of α_2 receptor agonists. It has a high specificity for α_2 receptor (α_2 :α_1 1600:1), when compared to clonidine (α_2:α_1 200:1).



Pharmacokinetics

Dexmedetomidine, the dextroisomer of medetomidine, is short acting with linear concentration dependent kinetics.

DISTRIBUTION

The pharmacokinetics of Dexmedetomidine is commonly described using a two-compartment model .It is rapidly distributed after administration with a half life of 6 minutes. The elimination half life is approximately 2 hours. Dexmedetomidine is highly bound to plasma proteins (94%) without significant variations in pharmacokinetic parameters between males and females[32].

METABOLISM AND ELIMINATION

Dexmedetomidine is extensively metabolised in the liver through glucuronide conjugation and biotransformation by the cytochrome P450 system without formation of toxic metabolites. The resulting methyl and glucuronide conjugates are excreted by the kidneys. Dexmedetomidine is metabolised by various metabolic pathways. Direct N-glucuronidation to inactive metabolites accounts for 41% of metabolism of Dexmedetomidine. N-methylation to produce 3-hydroxy N-methyl-Dexmedetomidine is the next major pathway accounting for 21% of metabolism of Dexmedetomidine. Hydroxylation followed by conjugation is the other metabolic pathway of Dexmedetomidine. Renal and hepatic diseases greatly impair the pharmacokinetic properties of Dexmedetomidine. Hepatic impairment results in an increase in the half-life of Dexmedetomidine as well as a decrease in clearance and protein binding. Renal dysfunction leads to a decrease in the elimination half-life, however the volume of distribution and clearance are not affected[33].

Molecular Weight	236.7 Daltons
Lipid solubility	30
Distribution t1/2	6 min
Protein Binding	94%
Volume of distribution	118 L
Elimination t1/2	120-180 min
Context sensitive half time	4 – 250 min

Pharmacodynamics

MECHANISM OF ACTION

The mechanism of action is unique and different from currently administered sedative agents. Dexmedetomidine acts by activation of α_2 adrenoceptors located in the presynaptic terminal and inhibits the release of norepinephrine. Activation of α_2 adrenoceptors in the post synaptic terminal in the CNS inhibits sympathetic activity and can cause sedation, anxiolysis, decreases shivering along with reduced heart rate and blood pressure. α_2 receptors inhibit adenylyl cyclase activity and result in decreased intracellular cyclic adenosine monophosphate(cAMP) levels. This inhibition of adenylyl cyclise activity is transduced by the inhibitory regulatory protein $G_{i..}$The α_2 agonists' actions are readily reversed by α_2 adrenergic antagonists (e.g.atipemazole) [34].

ANALGESIA

Dexmedetomidine has complex analgesic effects. There are two predominant mechanisms to achieve analgesia namely, activation of descending spinal inhibition and direct activation of presynaptic α2receptors on sensory afferent terminals in the dorsal horn. Analgesic effects are principally mediated through α_2 receptors when the drug is injected via intrathecal or epidural route[35].

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Dexmedetomidine has a sedative hypnotic effect and the unique feature is

that, patients are easy to wake up and can follow commands as it acts by sleep promoting pathways.

EFFECTS ON RESPIRATORY SYSTEM

Sedation producing concentrations of Dexmedetomidine produce a decrease in minute ventilation, but the ventilator responses of CO_2 are retained[36]. Higher concentrations produce a 20 % increase in $PaCO_2$.

EFFECTS ON CARDIOVASCULAR SYSTEM

α_2 agonists are characterized by decreased heart rate and systemic vascular resistance and indirectly decreased and systemic blood pressure.

Uses

(i) INTENSIVE CARE UNIT

Dexmedetomidine is used for sedation in mechanically ventilated patients and lesser amounts of opioids are required when dexmedetomidine is used instead of benzodiazepines. It produces unique characteristics of sedation with minimal respiratory depression. Also, Dexmedetomidine when used for sedation provides a more stable hemodynamics during weaning[37].

(ii) ANAESTHESIA

Dexmedetomidine has been used as a premedicant in doses of 0.3 - 0.6

μg/kg, reducing the requirements of intravenous and volatile anaesthetics and also attenuating the hemodynamic stress response to endotracheal intubation[38,39]. Dexmedetomidine is also used for sedation in patients for monitored anaesthesia care.

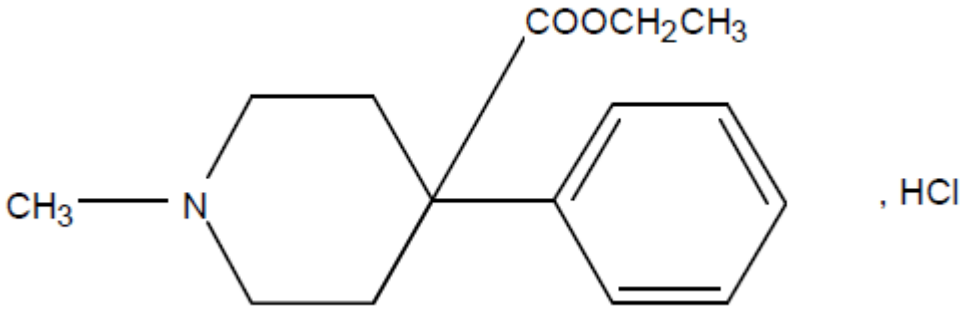
(iii) Antishivering agent

Dexmedetomidine is being used in a number of indications in intensive care unit settings as well as for analgesia and sedation either intra operatively or post operatively, its role in the prevention of shivering is studies in a few trials [40,41]. The anti-shivering effects of α_2 adrenoceptor agonists are mediated by binding to α2 receptors that mediate vasoconstriction and shivering. In addition to this, it has hypothalamic thermoregulatory effects[42]. Dexmedetomidine reduces the vasoconstriction and shivering thresholds. In other words, it prevents shivering by acting on the central thermoregulatory system rather than preventing shivering peripherally.

PETHIDINE

It is a synthetic opioid group of drug which has actions similar to morphine. It is a potent analgesic and can cause drowsiness, respiratory depression and sedation by its action on CNS. It exerts its action by acting opioid selective receptors.

Chemical name is ethyl1-methyl-4-phenylpiperidine-4-carboxylatehydrochloride.



Pharmacokinetics

Pethidine may be given as intramuscularly or intravenously. Analgesia persists for two to four hours. The drug is distributed extravascularly. Vd is 4.17L/Kg. plasma protein binding is around 60%. Pethidine is metabolised in the liver to pethidinic acid followed by conjugation with glucuronic acid. It also undergoes N-demethylation to norpethidine. Norpethidine has 50% potency of pethidine but can increase seizure potential by two fold. Elimination half life is 3.5hours but prolonged in cirrhotic patients.

Antishivering mechanism

Pethidine acts via opioid receptors, mainly κ receptor. The main mechanism of action of pethidine is by decreasing the shivering threshold twice when compared with vasoconstriction threshold. This special antishivering property of pethidine is because of the disproportionate decrease in the threshold of shivering. Pethidine also acts via κ receptors and decreases shivering. Pethidine is considered the gold standard in abolishing shivering in patients under anaesthesia. So, numerous studies have been conducted comparing pethidine with other drugs in the prevention and treatment of

shivering. It is administered at a dose of 0.5mg/kg for the treatment of shivering.

CONTRAINDICATIONS

1. Hypersensitivity
2. Head injury
3. Patients on monoamine oxidase inhibitors
4. Cardiac arrythmias
5. Respiratory depression
6. Convulsive states like status epilepticus
7. Severe hepatic insufficiency
8. Acute alcoholism

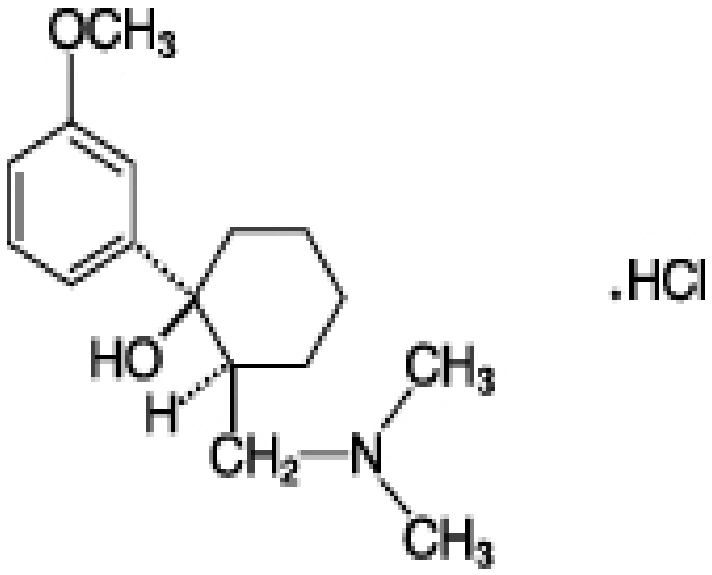
ADVERSE EFFECT

The most common and important adverse effect is respiratory depression which if severe can be reversed with naloxone 0.4mg I.V. But, mostly is self limited.

TRAMADOL

It is a synthetic opioid analgesic. It has two mechanisms of action. Inhibition of re-uptake of serotonin and nor epinephrine and binding to μ type of opioid receptor. Its analgesic potency is about one tenth that of morphine. Tramadol can cause analgesia, nausea, vomiting, dizziness etc., at therapeutic doses, it has no effect on heart rate or blood pressure.

Chemical name is (±)*cis*-2-[(dimethylamino)methyl]-1-(3methoxyphenyl) cyclohexanol hydrochloride.



Pharmacokinetics

Tramadol exists as a racemic (1:1) mixture of the (+) and (-)-enantiomer. Oral Bioavailability is 75%. Peak plasma concentration occurs at 2 hours. Vd is 2.6 L/kg. Plasma protein binding is approximately 20%. Tramadol is extensively metabolized by CYP2D6 and CYP 3A4. 30 % is excreted in urine as unchanged drug. The major metabolic pathway is N- and O- demethylation and glucuronidation. O- desmethyltramadol marked as M1is a pharmacologically active metabolite. Tramadol is eliminated primarily by liver and metabolites by kidney. The half life of tramadol is 6 hours and M1 is 7 hours.

Uses

It is a potent analgesic which is used for a number of post operative patients and also intra operatively for analgesia or sedation or as an antishivering agent. It is also used for treating chronic pain implications including cancer pain. Tramadol binds weakly with μ receptor while, M1 metabolite binds strongly. The anti-shivering action of tramadol is due to serotonergic and noradrenergic receptor activity and also opioid receptor activity. Because of serotonergic and noradrenergic receptor action, it acts by inhibiting descending spinal pathways. The mechanism of action of tramadol in the prevention of shivering is different from that of pethidine.

ADVERSE EFFECTS and CONTRAINDICATIONS

1. HYPERSENSTIVITY
2. Acute alcohol intoxication
3. Seizures
4. Nausea and vomiting around 70% incidence
5. Serotonin syndrome
6. Respiratory depression
7. Dizziness
8. Withdrawal symptoms
9. Substance abuse potential

CHAPTER 04

REVIEW OF LITERATURE

Lim fern et al [43](anaesthesia and analgesia 2015) conducted a study to find out the effectiveness of dexmedetomidine, pethidine and tramadol in the treatment of shivering after administration of spinal anaesthesia. Dexmedetomidine was administered at a dose of 0.5µg/kg, pethidine at 0.5mg/kg and tramadol at 0.5mg/kg.

Patients who developed shivering of grade 3 0r 4 intraoperatively was included in the study. Sample size was 60, 20 patients in each group and study drug was given after the onset of shivering as a slow intravenous bolus dose over 5 minutes. The time elapsed between the administration of the drug and cessation of shivering was noted. Any adverse effect during this period was also noted. If shivering does not stop even after 15 minutes, that was considered ineffective. Patients were also asked subjectively to grade the improvement after administration of drug as, "no improvement", "partial improvement" or "marked improvement".

Results were analysed. It was found that, response rate was highest in the dexmedetomidine group and was statistically significant with a P value of 0.0012. Pethidine and tramadol groups were similar with a slightly higher response rate with pethidine group but was statistically insignificant. The time required for cessation of shivering was almost the same in all groups and was around 7 minutes. The study concluded that dexmedetomidine was more efficient in the treatment of shivering but can cause bradycardia and hypotension while, pethidine and tramadol are equally efficient in the treatment

of shivering.

Mittal et al [44] (Indian journal of anaesthesia 2014) conducted a study comparing the efficacy of dexmedetomidine and tramadol in the treatment of post spinal anaesthesia shivering. Patients who developed shivering of grade 3 or more were randomly allocated to either dexmedetomidine group to receive 0.5µg/kg IV or tramadol 0.5mg/kg IV bolus. Patients who underwent either elective or emergency lower abdominal surgeries or orthopaedic or lower limb plastic surgeries were included in the study. Sample size was 50 with 25 in each group.

The time for the onset of shivering and the time for cessation of shivering after the administration of study drug, response rate, that is, cessation of shivering less than 15 minutes and the recurrence of shivering were all noted. It was found that the onset of shivering was similar in both groups. Complete cessation of shivering was faster with dexmedetomidine than tramadol with a statistically significant P value of 0.0024. Response rate was 100 % in both groups. Recurrence of shivering was higher in tramadol group.

They concluded the study that both dexmedetomidine and tramadol are equally effective in the treatment of post spinal anaesthesia shivering. The time taken for complete cessation of shivering was faster in dexmedetomidine group and sedation caused by dexmedetomidine provides additional comfort to the patient

Bozgeyik et al [45](Saudi journal of anaesthesia 2014), formulated a study to find the effectiveness of preemptive dexmedetomidine and tramadol

preventing post spinal anaesthesia shivering. Sample size was 90 with 30 in each group. Either dexmedetomidine 0.5µg/kg in 100 ml NS or tramadol 100 mg in 100 ml NS or 100 ml NS alone was given to patients who underwent elective knee arthroscopy procedures.

It was found that both dexmedetomidine and tramadol group patients had statistically significant shivering grades of 2 or less when compared with saline group (p=0.01). They concluded that, both dexmedetomidine and tramadol are equally efficient in the prevention of shivering but dexmedetomidine has an added advantage of sedation which prevents anxiety also.

Usta B et al [41](clinics 2011) evaluated the efficacy of dexmedetomidine in prevention of shivering after spinal anaesthesia. Sample size was 60. The study drug given was either dexmedetomidine at 1µg/kg IV followed by 0.4µg/kg IV infusion till the end of surgery or a placebo of normal saline will be given by infusion. If shivering of grade 3 or more occurs in less than 15 minutes of spinal anaesthesia, patients were given pethidine 25 mg. the incidence and severity of shivering was also assessed.

It was found during the study period that more patients in saline group needed pethidine and also the incidence and severity of shivering was also higher, P value was 0.001. The incidence of adverse reactions like hypotension and bradycardia were comparable between both groups and was statistically insignificant. They concluded the fact that perioperative administration of dexmedetomidine decreased the incidence and severity of shivering substantially. The sedation caused by dexmedetomidine is also convincing for

the patient intra operatively.

KIM et al [46](international journal of medical sciences 2013) conducted a study to identify the optimal dose of dexmedetomidine required for the control of post anaesthesia shivering. The study was conducted in 132 patients who underwent laparoscopic total hysterectomy under general anaesthesia. Patients were seperated into 4 groups to receive either normal saline or dexmedetomidine at 0.5µg/kg IV or dexmedetomidine 0.75µg/kg IV or dexmedetomidine1µg/kg IV. The incidence of shivering and time for extubation was monitored. The study drug was given 30 minutes before the anticipated end of the surgery.

It was found that extubation time was less in saline group compared with dexmedetomidine 0.75µg/kg group or dexmedetomidine 1µg/kg group. Almost 60 % of the patients in saline group had shivering after extubation. Whereas, only 10 % of the patients had shivering in dexmedetomidine 0.75µg/kg or 1µg/kg group. The need for rescue analgesia was also longer in dexmedetomidine 1µg/kg group. The incidence of shivering was more in dexmedetomidine 0.5µg/kg group around 35% and was statistically significant. It was concluded finally that dexmedetomidine at a dosage of 0.75µg/kg or 1µg/kg IV is optimal for the prevention of post anaesthesia shivering.

M.MOHTA et al [47](2009). The study was conducted to find out the dose of tramadol needed for a good anti shivering and analgesic action. Tramadol was administered intravenously at a dose of 1,2 and 3mg/kg in three groups and fourth group received pethidine at 0.5mg/kg and fifth group received normal saline. Sample size was 165. At the start of closure of the

wound, test drug was given in a 5 ml diluted solution. Results were analysed by chi square test.

Shivering was almost 40 % in saline group. In patients treated with tramadol 1mg/kg was only 9% and in tramadol 2mg/kg was 6% and in tramadol 3mg/kg was 12%. The requirement of analgesic was lesser in groups who received tramadol 2mg/kg and 3mg/kg when compared with pethidine group. The conclusion made from the study was that, tramadol at either 1, 2 or 3mg/kg is as effective in the prevention of shivering as pethidine at 0.5mg/kg. Tramadol at 2mg/kg is more ideal for the prevention of shivering and also as a good analgesic with minimum side effects.

Philip et al [48] (international journal of scientific study 2014)framed a double blinded study to compare the efficiency of tramadol and pethidine in the treatment of shivering in 127 patients who underwent surgeries under epidural anaesthesia. Out of these 127 patients, 60 patients developed shivering after administration of epidural anaesthesia and were included in the study and accommodated into two groups to receive either tramadol 1mg/kg or pethidine 0.5mg/kg intravenously as bolus. The time taken for the onset of shivering, time taken for the stopping of shivering, core temperatures and hemodynamic parameters were noted.

There was no significant difference in time taken for the onset of shivering but time for cessation of shivering was shorter in tramadol group when compared to pethidine group($p<0.05$). The core temperatures were similar in both groups. The recurrence rate was higher in pethidine than in tramadol group. Inferences made from the study were that, incidence of

shivering after epidural anaesthesia is approximately 60% and both tramadol and pethidine are effective in the treatment of shivering. The onset of action was faster with tramadol than with pethidine and recurrence rate was also higher with pethidine.

Dhimar et al [49] (Indian journal of anaesthesia 2007) conducted a study to identify the efficacy of tramadol in comparison with pethidine in the treatment of shivering during regional anaesthesia. 60 patients were enrolled into two groups and were given either tramadol 1mg/kg or pethidine 1mg/kg after the onset of shivering and time taken for the onset of disappearance of shivering and also for complete disappearance of shivering were noted. It was found that both time taken for onset of disappearance of shivering and complete disappearance of shivering was shorter with tramadol than pethidine and they finally concluded that tramadol has faster onset of action, better control of shivering and less recurrence and so, is superior in the treatment of shivering when compared with pethidine.

Tewari et al [50](journal of anaesthesiology clinical pharmacology 2014) conducted a study comparing the efficacy of oral clonidine and tramadol used preoperatively in order to control perioperative shivering in patients who underwent TURP surgery under spinal anaesthesia. The study was conducted in 120 patients divided in 3 groups with group A patients received oral clonidine 150µg, group B patients oral tramadol 50 mg and group C placebo. Parameters like patients who had shivering, grades of shivering and adverse effects were all noted.

It was found that, among patients of group A only 2 had shivering and in

group B only 3 had shivering while in group C, 16 patients had shivering of greater intensity and lasted longer. They concluded that oral tramadol and clonidine are equal in efficacy in controlling perioperative shivering in elderly patients under spinal anaesthesia post TURP.

Kim ya et al [51] compared the efficacy of nefopam with meperidine in prevention of shivering during spinal anaesthesia. 65 patients were enrolled in two groups and received either meperidine 0.4mg/kg or nefopam 0.15mg/kg. All drugs were given as infusion over 15 min before giving spinal anaesthesia. It was observed that the incidence and grades of shivering were similar in both the groups so it was concluded that nefopam which is a non opioid analgesic can be used as an alternate for meperidine in the prevention of shivering.

CHAPTER 05

MATERIALS AND METHODS

This study on patients undergoing lower abdominal surgeries and lower limb general surgeries under spinal anaesthesia was approved by the Institutional Ethical Committee, Stanley Medical College, Chennai. This was a prospective study conducted on 90 patients over a period of 3 months. Pre-anaesthetic evaluation was done, recording a detailed history and performing a complete physical examination. Complete blood count, renal function test, random blood sugar, HBsAg, HCV and anti retroviral screening tests were done. After discussion of anaesthetic options, a written preoperative consent was obtained.

SAMPLE SIZE AND RANDOMISATION

The sample size was calculated as 90 based on the pilot study and statistical reports of previous studies. The group sizes (n=30) were calculated to find out the efficiency of study drugs in prevention of shivering with a power of 90% [assuming a variability (sd) of ±10%] and a significance level of 0.05. The patients were randomly allocated into 3 groups of 30 each and were named as group D (Dexmedetomidine 0.5µg/kg), group T (Tramadol 0.5mg/kg) and group P (Pethidine 0.5mg/kg). The investigator prepared 90 lots numbered serially from 1-90. A coding sheet was also simultaneously prepared that allotted each number randomly to a group. The observer is allowed to take a lot and the selected number was marked in the proforma. Then the observer is blinded for drug being infused and performs the procedure. At the end of the study coding sheet was revealed. For the serial numbers which were selected and

excluded as per the exclusion criteria, the same serial number was mixed again in the lot by the investigator.

(i) INCLUSION CRITERIA

(a) ASA grade I or II

(b) Age 18 to 65 years

(c) Undergoing Spinal anaesthesia

(d) Lower abdominal surgeries and lower limb general surgeries.

(ii) EXCLUSION CRITERIA

a) known hypersensitivity or allergy to study drugs.

b) Cardio-pulmonary, renal or hepatic impairment.

c) known history of substance or alcohol abuse

d) patients who received any pre-medication

e) an initial core temperature >37.5˚C or <35.5˚C

f) blood transfusion during surgery

g) hypo- or hyperthyroidism

h) convulsions or psychiatric disorder

i) patient refusal

j) pregnancy and lactation

MATERIALS

The following equipments, drugs and monitors were kept ready for the conduct of anaesthesia.

EQUIPMENTS

1. 18Gauge IV cannula
2. Sterile towels and gauze packs
3. Sterile gloves
4. Surgical Spirit Solution
5. Sponge holding forceps
6. 2 ml and 5 ml syringes
7. 25G quincke needle
8. IV fluids
9. 100ml Normal saline with study drugs

DRUGS

1. Inj.Dexmedetomidine 0.5µg/kg
2. Inj.Pethidine 0.5mg/kg
3. Inj.Tramadol 0.5mg/kg
4. Inj.Ondansetron 4mg
5. 15 mg of 0.5% hyperbaric bupivacaine
6. 2ml of 2% lignocaine for local infiltration

MONITORS

A multi parameter monitor with following was made available

1. Electrocardiography
2. Non-invasive Blood Pressure
3. Pulse Oximetry
4. Axillary Temperature

The following emergency drugs and equipment was kept ready.

1. Atropine
2. Adrenaline
3. Ephedrine
4. Laryngoscope with all sizes of blades.
5. Endotracheal Tubes
6. Oropharyngeal airways
7. Oxygen source
8. Suction Apparatus

Methodology

90 consented patients of age group 18 – 65 years belonging to American society of anaesthesiologists class I or II and posted for lower abdominal surgeries and lower limb general surgeries under spinal anaesthesia were randomly allocated to any one of the three groups :

1. Inj.Dexmedetomidine 0.5µg/kg in 100 ml NS

2. Inj.Pethidine 0.5mg/kg in 100 ml NS
3. Inj.Tramadol 0.5mg/kg in 100 ml NS

PROCEDURE

Patients were shifted to the operation theatre, monitors were connected (pulse oximetry, electrocardiography, temperature and non-invasive arterial blood pressure monitoring), intravenous (IV) access was secured with 18-G cannula and patients were preloaded with RL at 10ml/kg over 15 mins. The operation room temperature was maintained at 25 ^{0}C. All the patients were covered by a single layer of surgical drapes, exposing only the surgical site. IV fluids were used at the operation room temperature.

All the patients were placed in the right lateral decubitus position and under strict aseptic precautions, subarachnoid block performed in L3-4 interspace after infiltrating skin with 2 ml of 2% lignocaine. 25G quincke needle was inserted intrathecally and 15mg of 0.5% hyperbaric bupivacaine (3ml) injected after checking for free flow of clear CSF.

Patients were turned to supine position and infusion of the study drug in 100ml NS by a blinded observer over 10 minutes in a three way adapter along with IV fluid administration at 6ml/kg/hr. Oxygen via face mask at 5L/min was administered to all the subjects. Inj.Ondansetron 4mg IV was given to all the patients. Surgery will commence when the level of sensory block reaches T8. Patients were monitored for a period of 120 minutes or the end of the surgery whichever was longer.

Shivering was monitored by a grading system as described by **wrench**[52]

1. Grade 0: No shivering,
2. Grade 1: One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity,
3. Grade 2: Visible muscle activity confined to one muscle group,
4. Grade 3: Visible muscle activity in more than 1 muscle group
5. Grade 4: Gross muscle activity involving the whole body

Sedation was assessed by a four point scale as per **Filos et al**[53]

1. Grade 1: Awake and alert,
2. Grade 2: Drowsy, responsive to verbal stimuli,
3. Grade 3: Drowsy, arousable to physical stimuli,
4. Grade 4: Unarousable

Patient's baseline Heart rate, Blood pressure, Temperature and SpO_2 was monitored and monitoring of all these parameters were done for every 5minutes till 15 minutes and then every 15 minutes till 120 minutes.

Hypotension was defined as a systolic blood pressure of less than 90mmHg or a diastolic blood pressure of less than 60mmHg and will be treated with Inj.ephedrine 6mg IV. Bradycardia was defined as a heart rate of less than 60 beats per minute and will be treated with Inj.Atropine 0.6mg IV. Patients who developed shivering during the study period were given Inj.Pethidine 0.25mg/kg IV bolus as rescue drug. Any other adverse effects during the study period was noted. The statistical analysis was done by statistical software package SPSS 22.0 using chisquare test and ANOVA.

CHAPTER 06

Observation and Results

1.Age

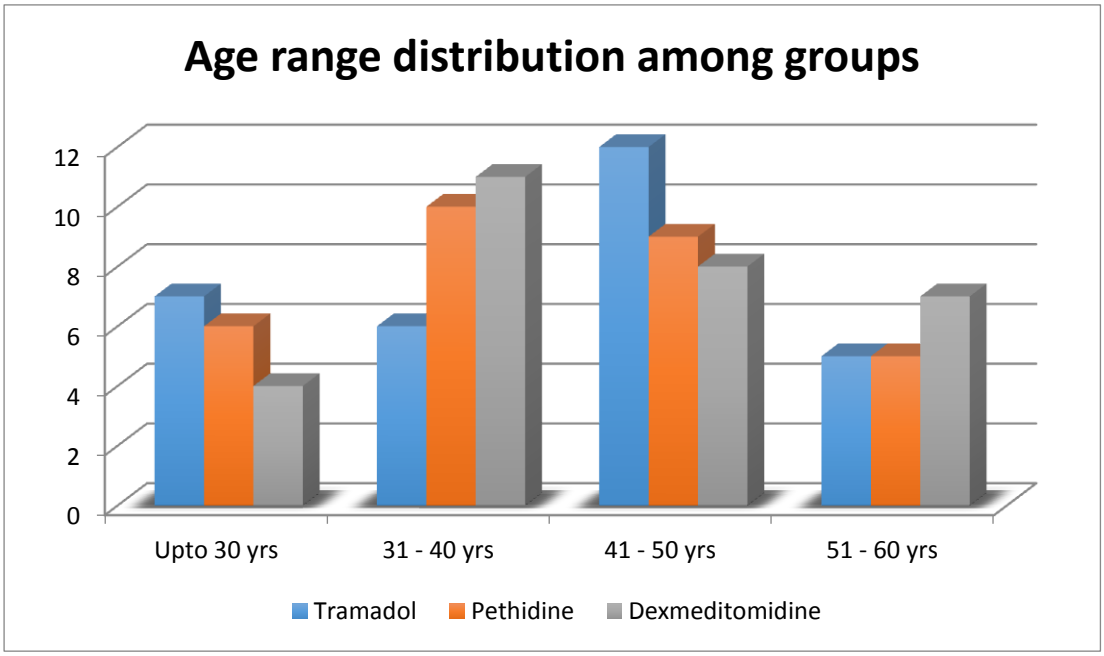


Figure 8 : Age distribution between study groups

Age	Tramadol	Dexmedetomidine	Pethidine
Upto 30yrs	7 (23.3%)	4 (13.3%)	6 (20%)
31-40 yrs	6 (20%)	11 (36.7%)	10 (33.3%)
41-50 yrs	12 (40%)	8 (26.7%)	9 (30%)
51–60 yrs	5 (16.7%)	7 (23.3%)	5 (16.7%)

Table 1: Age distribution between groups

Most of the patients in the study belonged to age group 41-50 years. In the age group of less than 30 years, 7 patients were given tramadol, 6 patients were given pethidine, 4 patients were given dexmedetomidine. In the age group of 31-40 years, 6 patients were given tramadol, 10 patients were given pethidine, 11 patients were given dexmedetomidine. In the age group of 41-50 years, 12 patients were given tramadol, 9 patients were given pethidine, 8 patients were given dexmedetomidine. In the age group of 51-60 years, 5 patients were given tramadol, 5 patients were given pethidine, 7 patients were given dexmedetomidine.

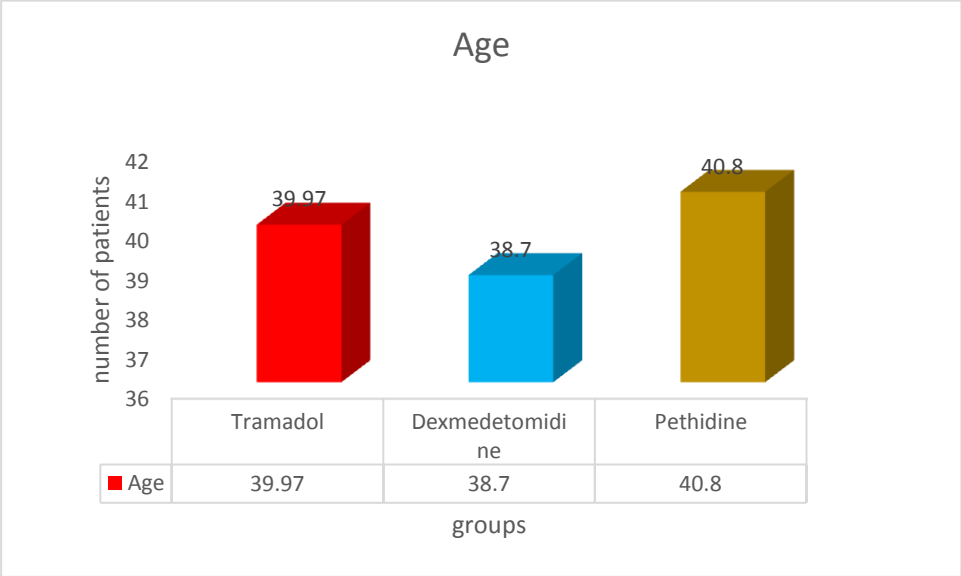


Figure 9 : Mean age group of study population

	Tramadol	Dexmedetomidine	Pethidine	P value
Age	39.97 ± 9.84	38.70 ± 9.64	40.80 ± 9.81	0.715

Table 2 : Mean age group of study population

Mean age of patients in tramadol group was 39.97 years, in dexmedetomidine group it was 38.70 years and in pethidine group, it was 40.80. P value was 0.715. Hence, not statistically significant.

2. Sex

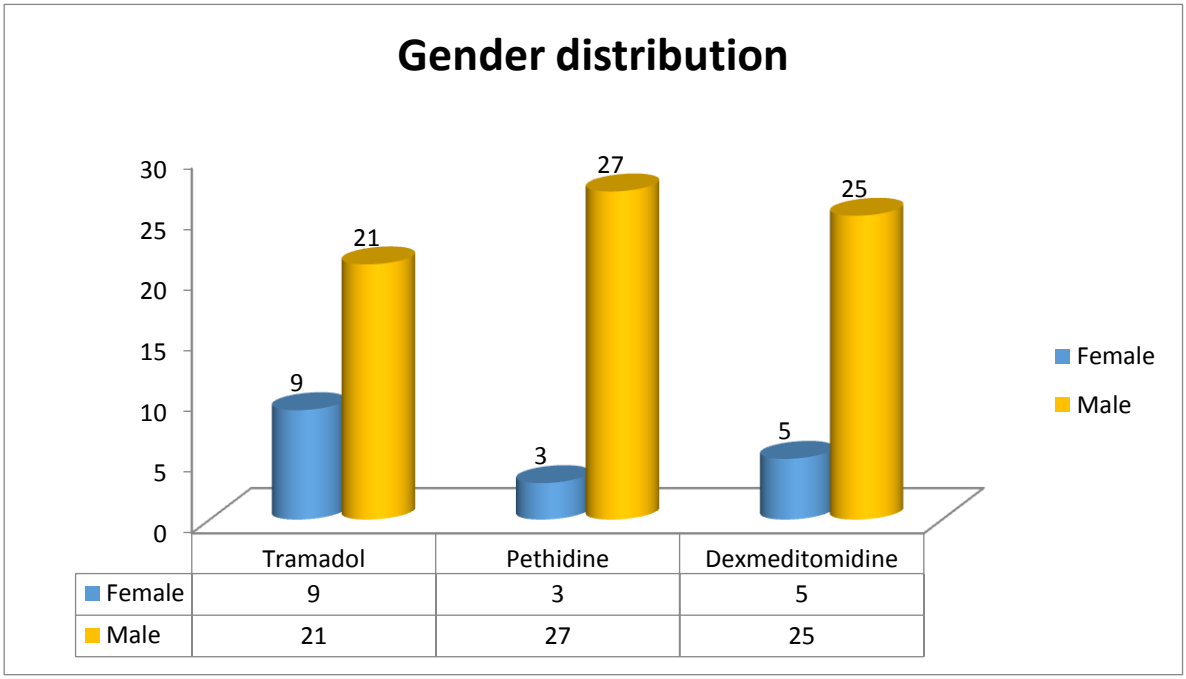


Figure 10 : sex distribution between groups

Sex	Tramadol	Dexmedetomidine	Pethidine
Male	21 (23.3%)	25 (27.8%)	27 (30%)
Female	9 (10%)	5 (5.5%)	3 (3.3%)

Table 3 : **sex distribution between groups**

Number of male patients were 21 in tramadol group, 25 in dexmedetomidine group and 27 in pethidine group. Number of female patients were 9 in tramadol group, 5 in dexmedetomidine group and 3 in pethidine group. P value is 0.131, hence not statistically significant.

3. Height

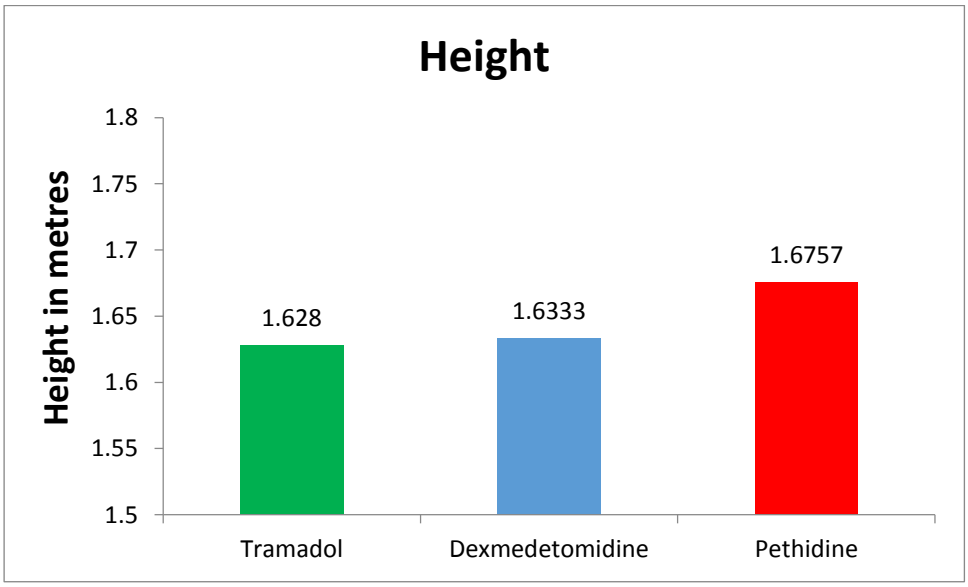


Figure 11 : Comparison of height between study groups

	Tramadol	Dexmedetomidine	Pethidine	P value
Height	1.628	1.6333	1.6757	0.628

Table 4 : Comparison of height between study groups

The mean height of patients in the tramadol group was 1.628, dexmedetomidine group was 1.6333 and pethidine group was 1.6757 and the P value is 0.628 which is not statistically significant.

4. ASA status

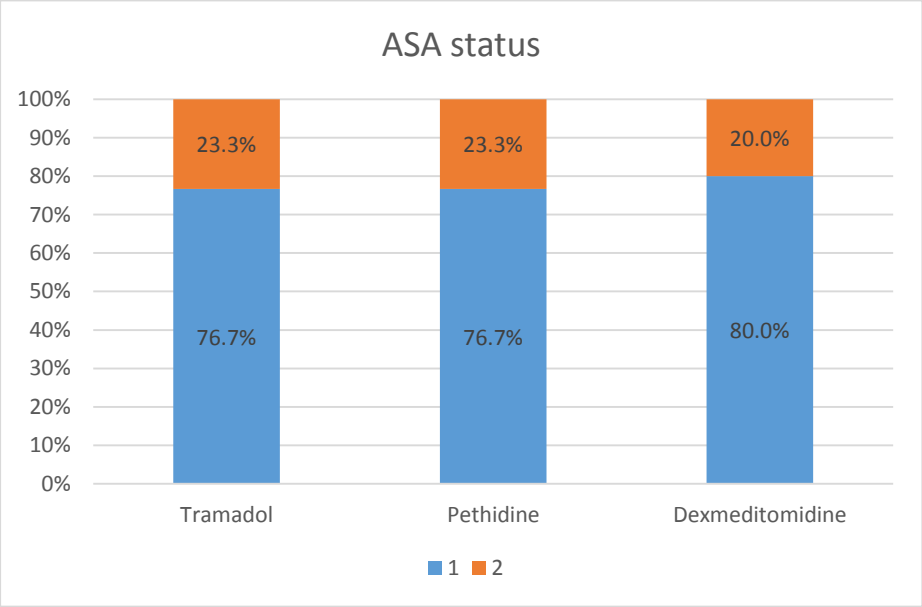


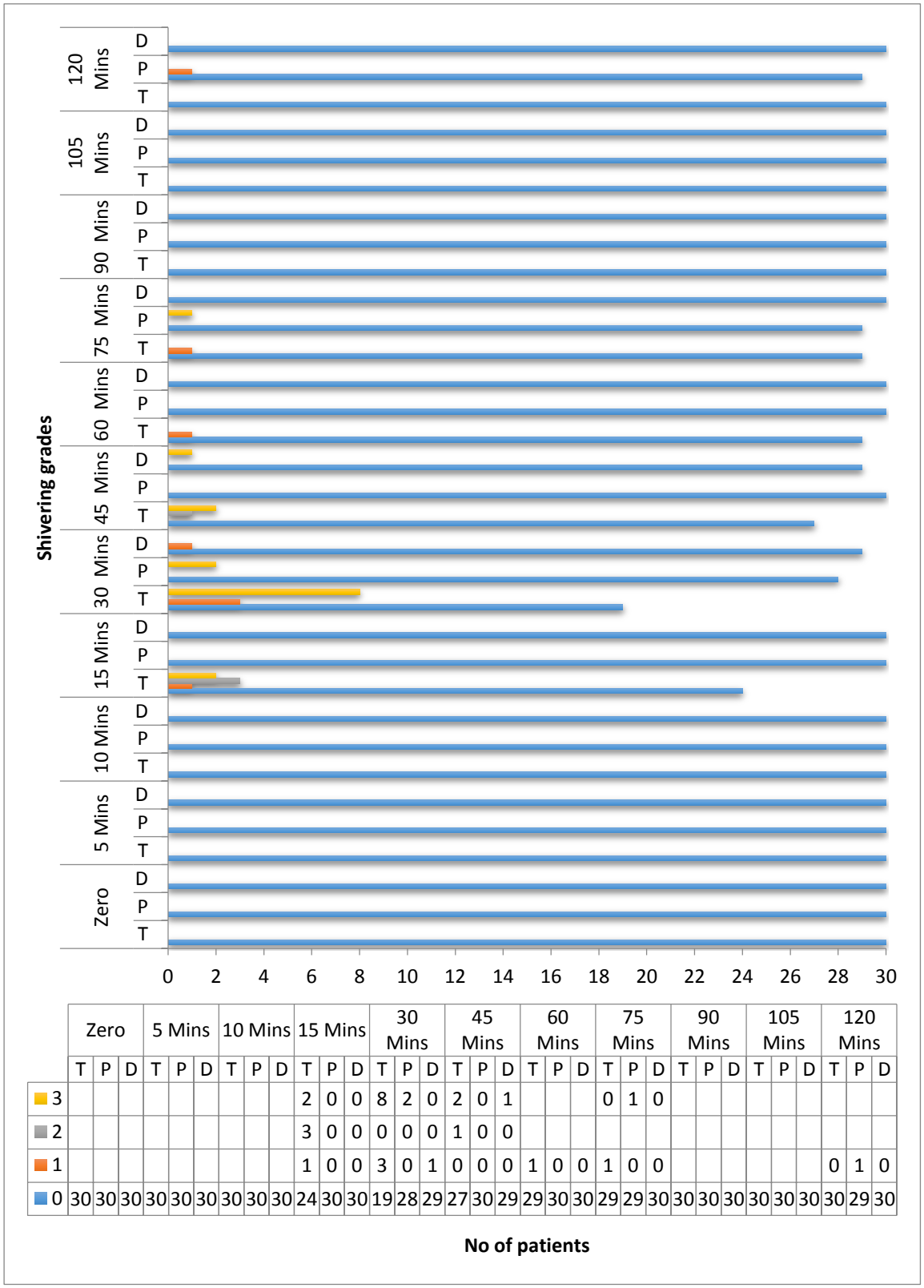
Figure 12 : Comparison of ASA status between groups

ASA	Tramadol	Pethidine	Dexmedetomidine
I	23 (76.7%)	23(76.7%)	24(80%)
II	7(23.3%)	7(23.3%)	6(20%)

Table 5 : Comparison of ASA status between groups

The number of patients who belong to ASA I were 23 in tramadol group, 23 in pethidine group and 24 in dexmedetomidine group. The number of patients who belong to ASA II were & in tramadol group, 7 in pethidine group and 6 in dexmedetomidine group. P value for this is 0.938 and hence, not significant.

5. Shivering grades



	Zero			5 Mins			10 Mins			15 Mins			30 Mins			45 Mins			60 Mins			75 Mins			90 Mins			105 Mins			120 Mins		
	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D
3										2	0	0	8	2	0	2	0	1				0	1	0									
2										3	0	0	0	0	0	1	0	0															
1										1	0	0	3	0	1	0	0	0	1	0	0	1	0	0							0	1	0
0	30	30	30	30	30	30	30	30	30	24	30	30	19	28	29	27	30	29	29	30	30	29	29	30	30	30	30	30	30	30	30	29	30

Figure 13 : Grades of shivering in three groups

Time(mins)	Tramadol	Pethidine	Dexmedetomidine	P value
0	0	0	0	
5	0	0	0	
10	0	0	0	
15	6	0	0	0.045
30	11	2	1	0.003
45	3	0	1	0.384
60	1	0	0	0.364
75	1	1	0	0.403
90	0	0	0	
105	0	0	0	
120	0	1	0	0.364

Table 6 : Number of patients who had shivering

None of the patient in any of the groups had shivering at 0,5 and 10 minutes. In tramadol group, at 15 minutes, 2 patients had shivering of grade 3, 3patients had shivering of grade 2 and 1 patient had shivering of grade 1. In other 2 groups, there was no shivering. At 30 minutes, 8 patients in tramadol group had grade 3 shivering and 3 patients had grade 1 shivering, while in pethidine group, 2 patients had grade 3 shivering and in dexmedetomidine group, 1 patient had grade 1 shivering.

At 45 minutes, 2 patients in tramadol group had grade 3 shivering and 1 had grade 1 shivering, no patients in pethidine group had shivering, 1 patient in dexmedetomidine group had grade 3 shivering. At 60 minutes, 1 patient in tramadol group had grade 1 shivering, no patients in other groups had shivering. At 75 minutes, 1 patient in tramadol group had grade 1 shivering, 1 patient in pethidine group had grade 3 shivering and no patient in dexmedetomidine group had no shivering.

At 90 minutes and 105 minutes no patient had shivering. At 120 mins, 1 patient in pethidine group had grade 1 shivering, patients in other groups had no shivering. P value at 15 minutes is 0.045 which is <0.05 and is statistically significant. P value at 30 minutes is 0.003 which is <0.01 and so, highly significant. P value at other duration are not significant.

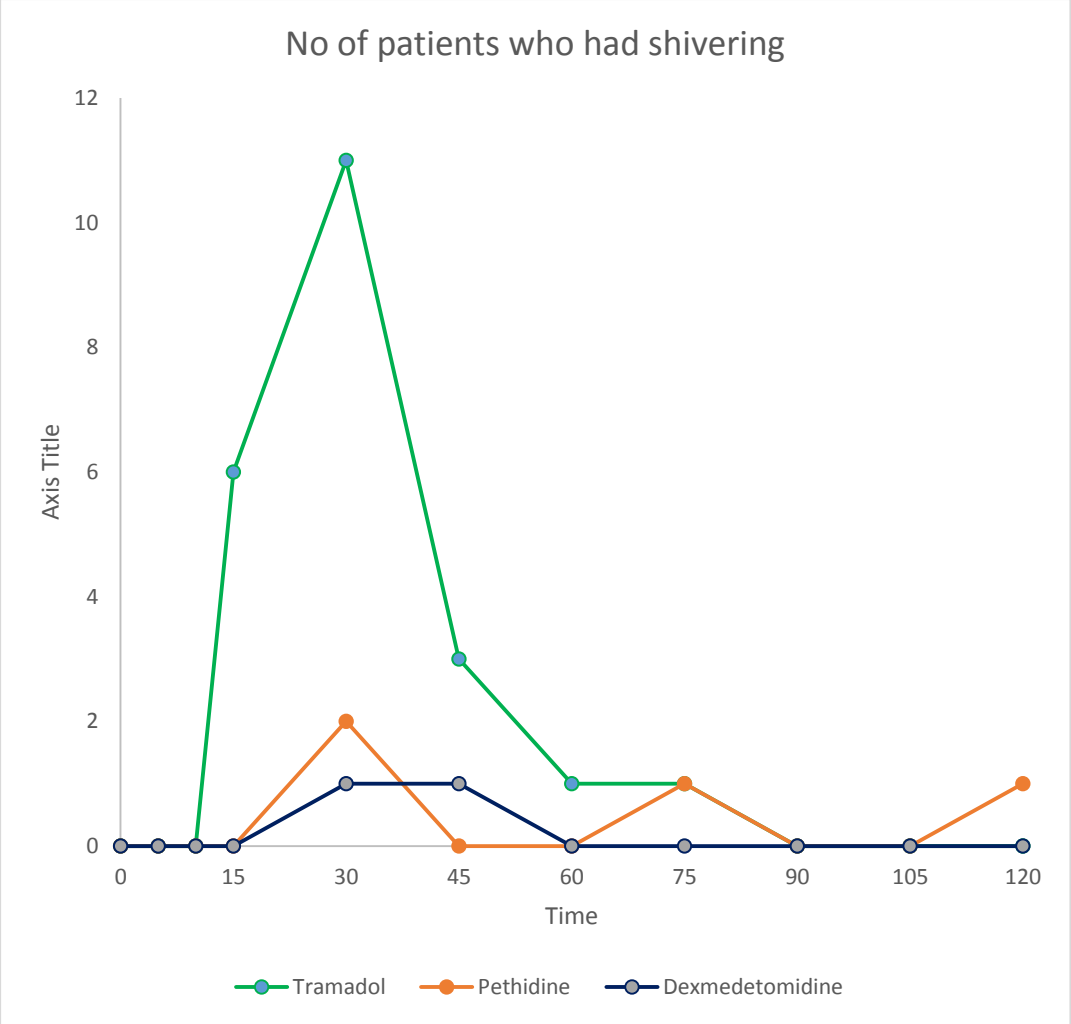
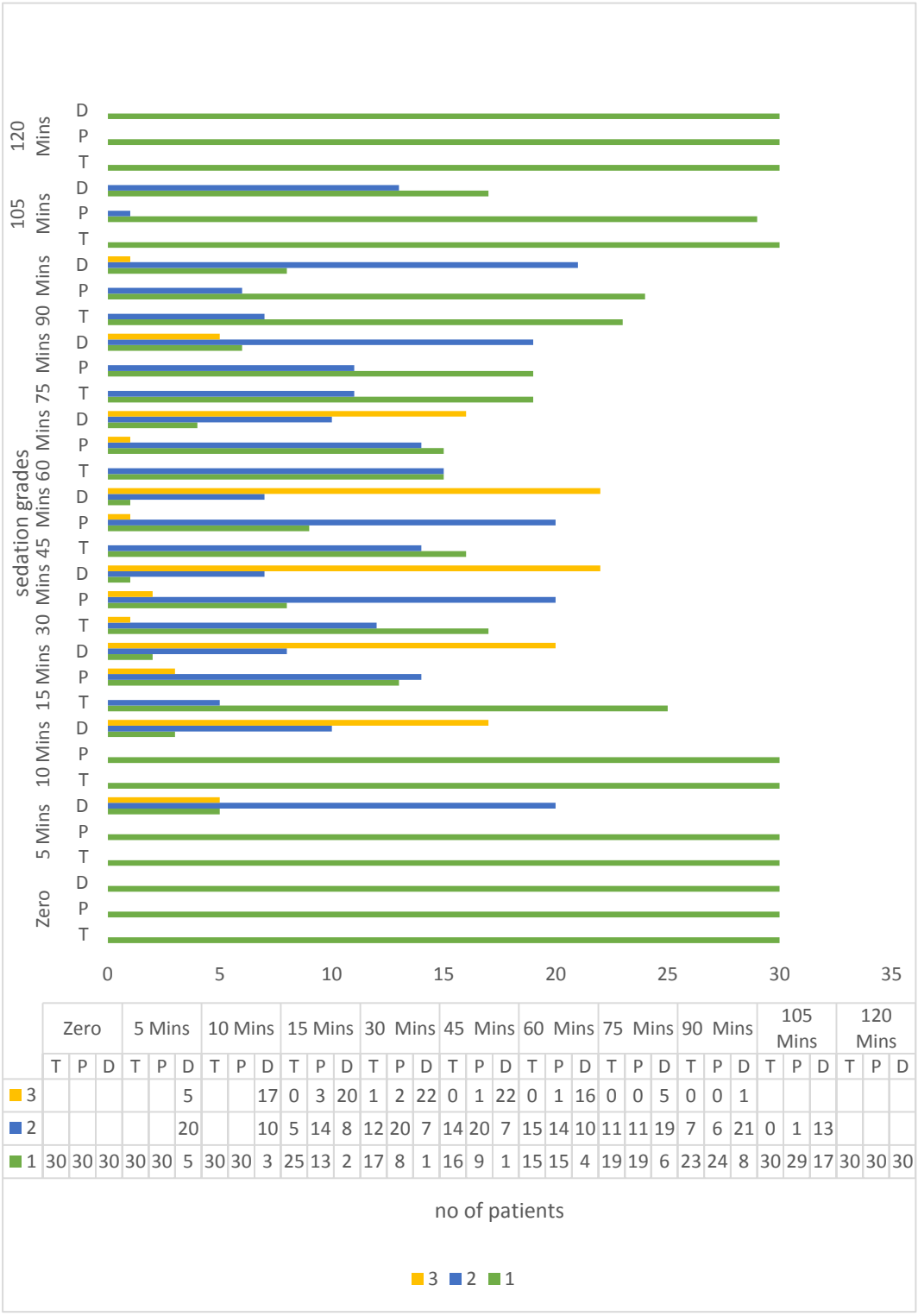


Figure 14 : No of patients who had shivering

6. Sedation



	Zero			5 Mins			10 Mins			15 Mins			30 Mins			45 Mins			60 Mins			75 Mins			90 Mins			105 Mins			120 Mins		
	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D	T	P	D
3						5			17	0	3	20	1	2	22	0	1	22	0	1	16	0	0	5	0	0	1						
2						20			10	5	14	8	12	20	7	14	20	7	15	14	10	11	11	19	7	6	21	0	1	13			
1	30	30	30	30	30	5	30	30	3	25	13	2	17	8	1	16	9	1	15	15	4	19	19	6	23	24	8	30	29	17	30	30	30

Figure 15 : Grades of sedation

Time(mins)	Tramadol	Pethidine	Dexmedetomidine	P value
0	0	0	0	
5	0	0	25	0.000
10	0	0	27	0.000
15	5	17	28	0.000
30	13	22	29	0.004
45	14	21	29	0.008
60	15	15	26	0.000
75	11	11	24	0.000
90	7	6	22	0.000
105	0	1	13	0.000
120	0	0	0	

Table 7 : No of patients sedated

At 5 minutes, no patients in tramadol and pethidine group had sedation but in dexmedetomidine group, 20 patients had grade 2 sedation and 5 had grade 3 sedation scores. At 10 minutes, no patients in tramadol and pethidine group had sedation, in dexmedetomidine group, 10 patients had grade 2 sedation and 17 patient had grade 3 sedation. At 15 minutes, 5 patients in tramadol group had grade 2 sedation, in pethidine group, 14 and 3 patients had grade 2 and 3 sedation respectively, in dexmedetomidine

group, 8 and 20 patients had grade 2 and 3 sedation respectively. At 30 minutes, in tramadol group, 12 and 1 patient had grade 2 and 3 sedation respectively, in pethidine group, 20 and 2 patients had grade 2 and 3 sedation respectively. In dexmedetomidine group, 7 and 22 patients had grade 2 and 3 sedation respectively.

At 45 minutes, in tramadol group, 14 patient had grade 2 sedation, in pethidine group, 20 and 1 patient had grade 2 and 3 sedation scores, in dexmedetomidine group, 7 and 22 patients had grade 2 and 3 sedation respectively. At 60 minutes, 15 patients in tramadol group had grade 2 sedation, in pethidine group, 14 patient had grade 2 and 1 had grade 3 sedation, in dexmedetomidine group, 10 patient had grade 2 and 18 grade 3 sedation scores.

At 75 minutes, 11 patients in tramadol and pethidine group had sedation score of 2 and in dexmedetomidine group, 19 had grade 2 and 5 had grade 3 sedation. At 90 minutes, in tramadol group, 7 patients had sedation score of 2, in pethidine group, 6 patients had sedation score of 2 and in dexmedetomidine group, 21 patients had score 2 and 1 had score of 3. At 105 minutes, all patients in tramadol group had sedation score of 1, only 1 patient in pethidine group had a score of 2 and 13 patients in dexmedetomidine group had a score of 2. At 120 minutes, no patient had sedation score greater than one. The P value was highly significant from 15 minutes till 105 minutes.

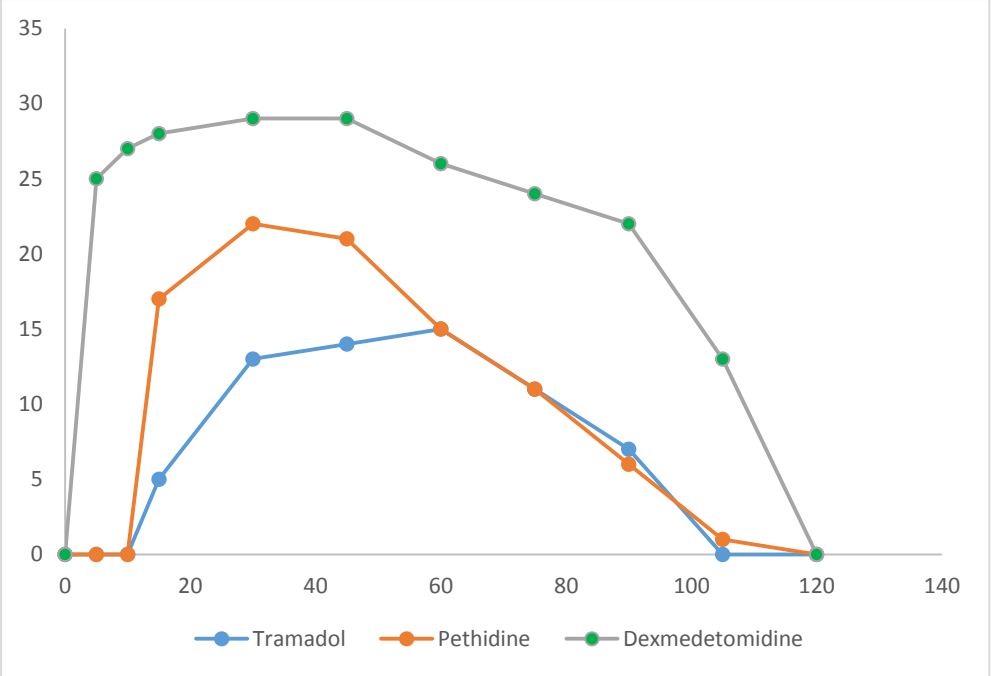


Figure 16 : No of patients sedated

7. Heart rate

Time	Tramadol	Pethidine	Dexmedetomidine	P value
0	82.53	82.47	84.03	0.784
5	80.40	81.23	82.70	0.585
10	79.67	82.13	81.17	0.316
15	82.00	80.37	77.80	0.241
30	81.97	79.27	80.27	0.332
45	81.30	80.33	79.80	0.739
60	80.33	80.83	80.27	0.955
75	80.13	81.33	79.27	0.556

Time	Tramadol	Pethidine	Dexmedetomidine	P value
90	80.43	80.57	77.90	0.255
105	78.63	80.60	78.13	0.351
120	79.23	79.77	78.47	0.785

Table 8 : Heart rate variation between the groups

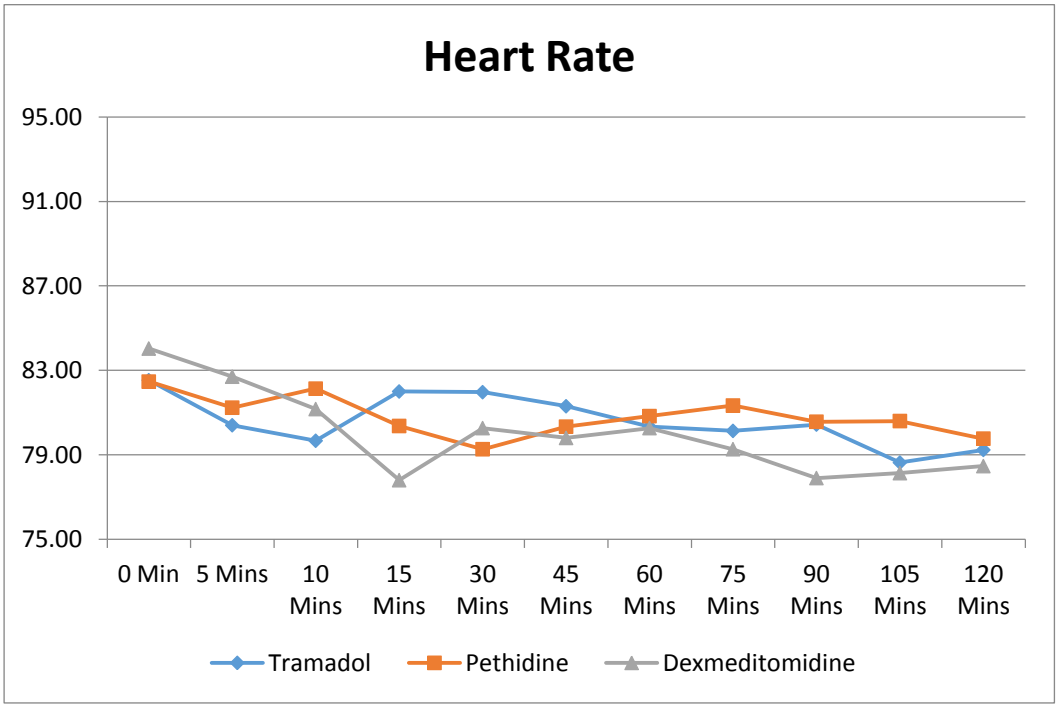


Figure 17 : Heart rate variation between the groups

The mean heart rate was similar in all the three groups with mean heart rate around 80 beats per minute. The P value is > 0.05 and hence, not significant.

8. Systolic Blood Pressure

Time	Tramadol	Pethidine	Dexmedetomidine	P value
0	126.7	124.3	125.2	0.489
5	123.4	120.7	121.7	0.419
10	115.4	114.8	113.4	0.775
15	118.7	118.0	116.3	0.724
30	119.5	118.6	118.8	0.938
45	121.4	119.6	121.3	0.584
60	122.1	121.2	123.2	0.429
75	120.9	121.1	122.6	0.612
90	120.8	122.3	120.3	0.570
105	121.4	121.9	121.2	0.937
120	119.9	120.7	121.1	0.778

Table 9 : Systolic blood pressure variation between the groups

The systolic blood pressure was comparable between all the three groups with insignificant P values. The systolic blood pressure mean varied around 120 mmHg and was similar in all the three groups.

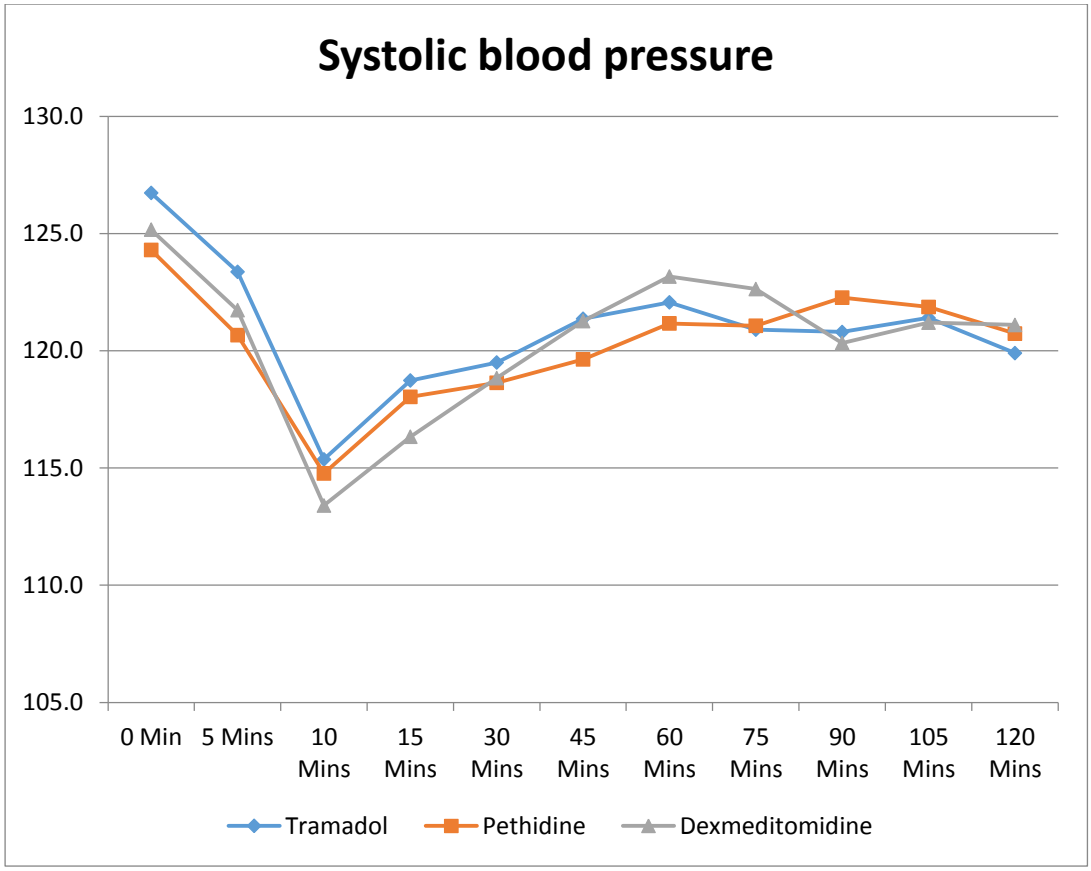


Figure 18 : Systolic blood pressure variation between the groups

9. Diastolic Blood Pressure

Time	Tramadol	Pethidine	Dexmedetomidine	P value
0	75.5	76.7	76.1	0.778
5	72.8	73.7	73.1	0.840
10	68.7	69.9	70.4	0.660
15	71.7	72.5	72.7	0.386
30	71.5	72.8	74.0	0.490
45	72.2	72.0	73.7	0.265

Time	Tramadol	Pethidine	Dexmedetomidine	P value
60	72.3	71.6	73.8	0.239
75	72.8	71.6	74.3	0.663
90	72.6	71.9	73.1	0.268
105	72.2	71.2	73.3	0.851
120	73.3	72.6	72.7	0.884

Table 10 : Diastolic blood pressure variation between the groups

.

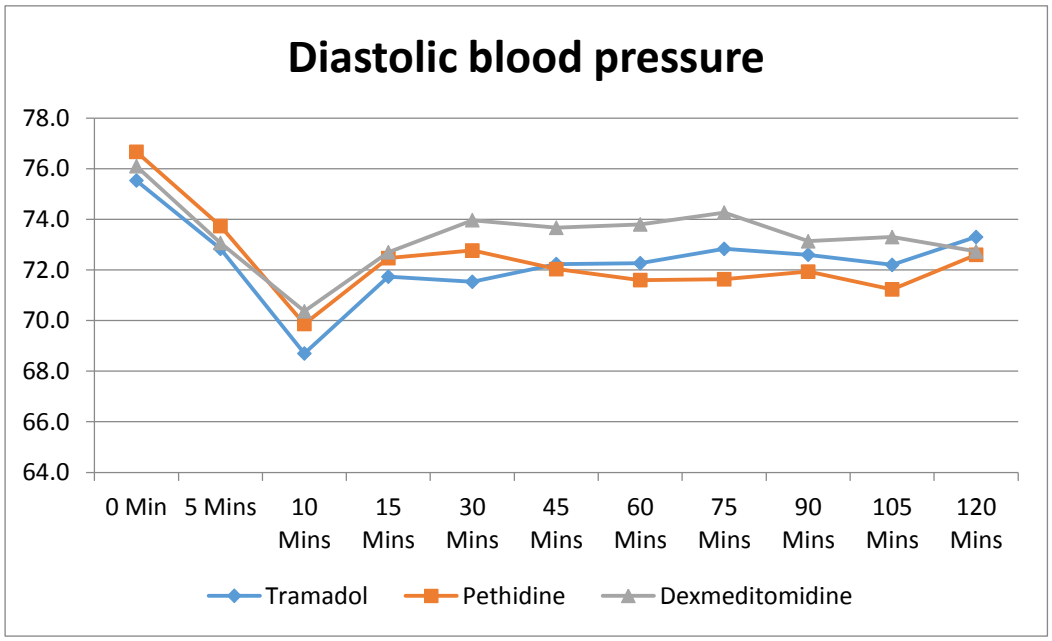


Figure 19 : Diastolic blood pressure variation between the groups

There mean diastolic blood pressure among was around 70 mmHg and was similar with statistically insignificant variation between the three groups..

10. Mean arterial pressure

Time	Tramadol	Pethidine	Dexmedetomidine	P value
0	119.5	119.8	119.5	0.981
5	116.4	116.6	116.3	0.985
10	87.4	87.7	85.8	0.452
15	90.2	90.7	88.7	0.464
30	88.3	88.2	88.9	0.905
45	88.4	88.9	90.4	0.344
60	88.5	88.4	90.0	0.389
75	88.4	88.5	89.3	0.730
90	89.0	88.4	89.9	0.489
105	88.4	88.2	89.1	0.700
120	73.3	73.0	74.2	0.596

Table 10 : Mean arterial pressure variation between the groups

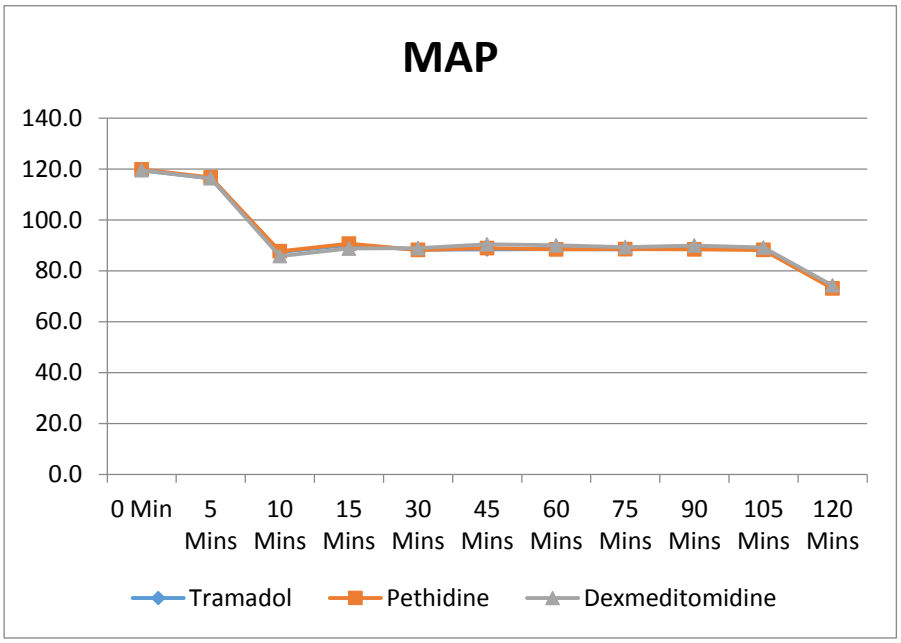


Figure 20 : Mean arterial pressure variation between the groups

In this study, the mean arterial pressure is comparable among all the three groups and there is no statistically significant differences among them.

11. Temperature

Time	Tramadol	Pethidine	Dexmedetomidine	P value
0	36.21	36.29	36.29	0.130
5	36.18	36.15	36.15	0.671
10	36.21	36.22	36.19	0.759
15	36.03	36.10	35.98	0.560
30	36.09	36.03	36.03	0.637
45	36.13	36.15	36.18	0.727
60	36.21	36.13	36.19	0.367
75	36.12	36.22	36.28	0.098
90	36.20	36.34	36.34	0.092
105	36.31	36.28	36.28	0.856
120	36.40	36.39	36.34	0.516

Table 12 : Mean axillary temperature between the groups

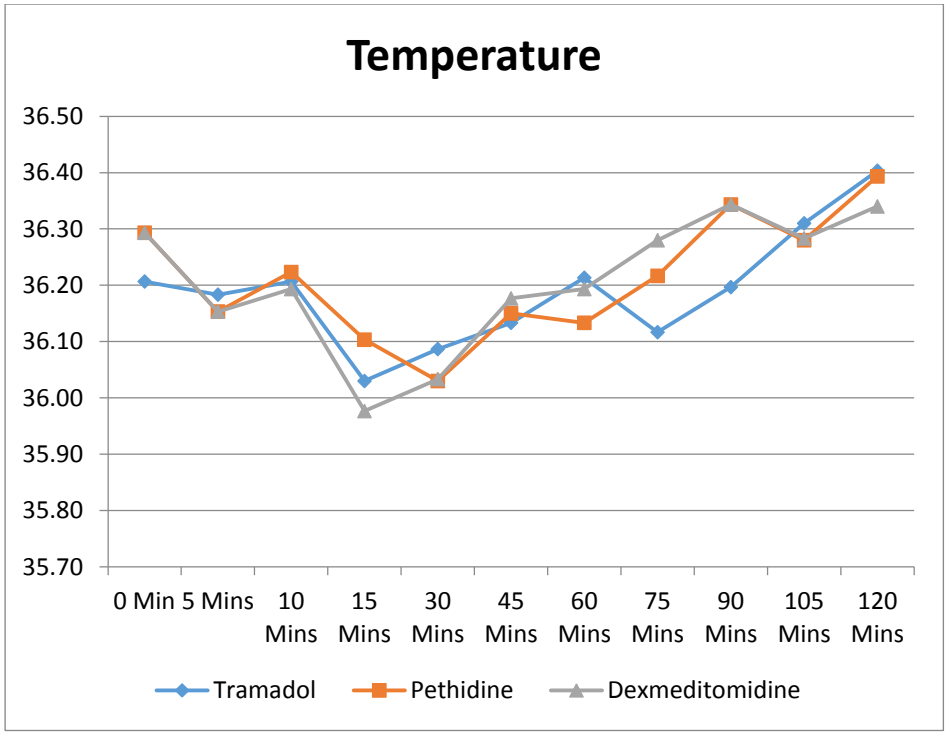


Figure 21 : Mean axillary temperature between the three groups.

The axillary temperature measured during the study in all the three groups showed comparable values with insignificant P values.

12. Rescue drug

Rescue	Tramadol	Pethidine	Dexmedetomidine
Yes	12	3	1
No	18	27	29

Table 13 : Rescue drug usage

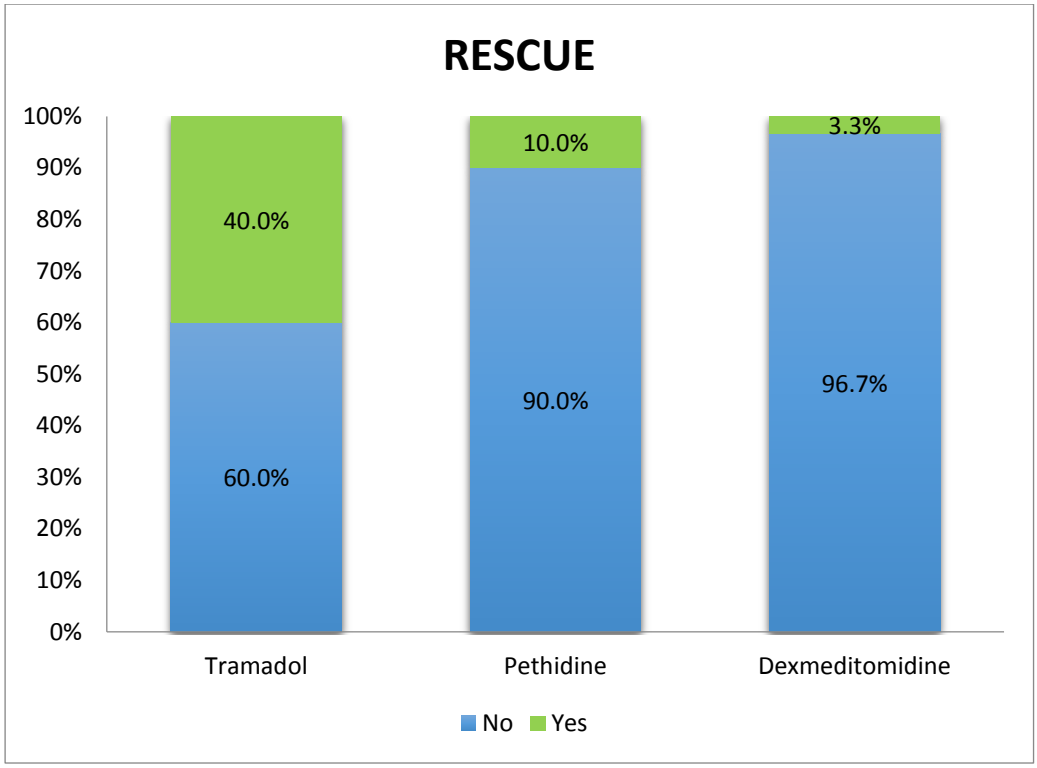


Figure 22 : Rescue drug usage

In this study, 12 patients (40%) needed additional rescue anti shivering drug in tramadol group. 3 patients in pethidine group and one patient in dexmedetomidine group required rescue drug. The P value for this is 0.001 which is highly significant.

13. Hypotension

In this study, 2 patients from dexmedetomidine group had a fall in systolic blood pressure to less than 90 mm Hg during the study period. Patients in other groups did not have any hypotension. The P value for this is 0.715 which is not significant.

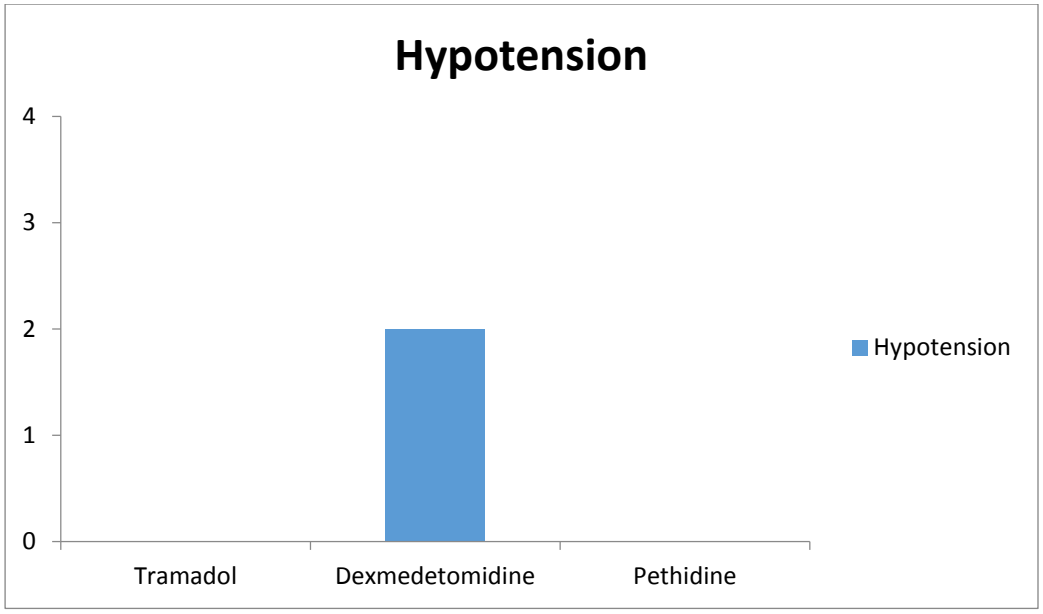


Figure 23 : Hypotension during the study

Tramadol	Dexmedetomidine	Pethidine	P value
0	2	0	0.715

Table 14 : Hypotension during the study

14. Bradycardia

In this study, no patient from tramadol group or pethidine group had bradycardia, but, three patients from dexmedetomidine group had a fall in heart rate of less than 60 beats per minute. The P value is 0.067 which is not statistically significant.

Tramadol	Dexmedetomidine	Pethidine	P value
0	3	0	0.067

Table 15 : Bradycardia during the study

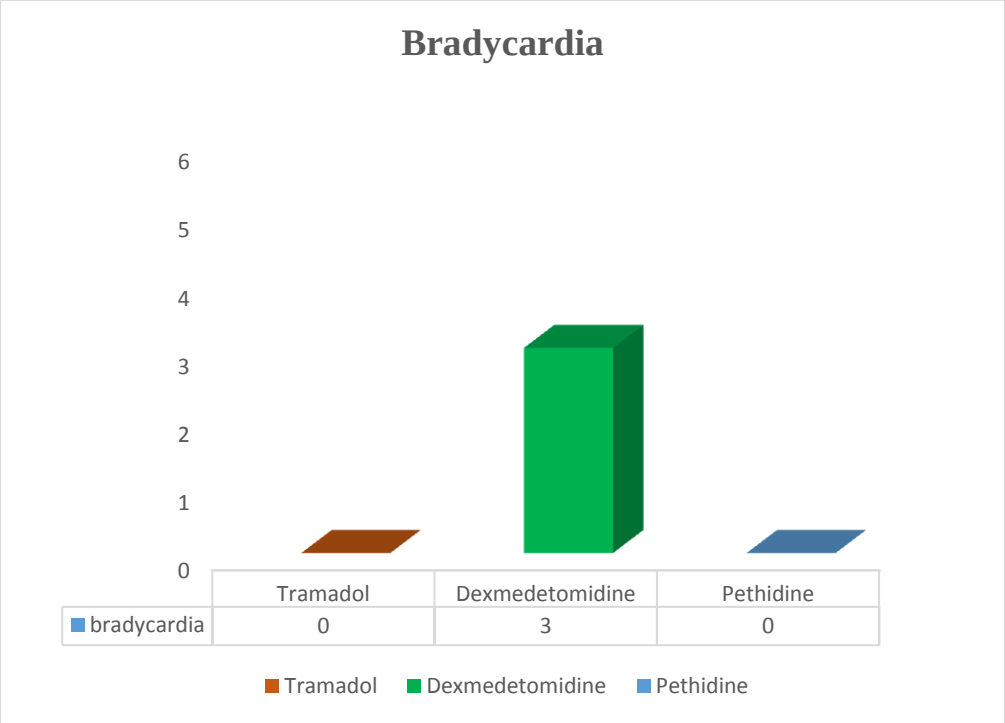


Figure 24 : Bradycardia during the study

CHAPTER 07

Discussion

Lower abdominal and lower limb surgeries are usually done under spinal anaesthesia. The ease and safety profile compared with general anaesthesia makes spinal anaesthesia the procedure of choice whenever possible. The most common surgical procedures done under spinal anaesthesia include inguinal hernioplasty, Trendelenburg procedure for varicose veins, excision and eversion of sac for hydrocele, split skin grafting in lower limbs, appendicectomy, hemorrhoidectomy, lateral anal sphincterotomy etc., In our current study, most of the surgeries done were hernioplasty, excision and eversion of sac for hydrocele, Trendelenburg procedure for varicose veins.

One of the least addressed and a very distressing complaint in many of the patients is shivering during the surgery and in the immediate postoperative period. The reason for shivering during spinal anaesthesia is multiple. If patients are uncomfortable it will lead to agitation of the patient. A number of steps are usually taken to prevent shivering during the surgery and one important step is administration of drugs to prevent shivering during surgery.

Since the time the technique of spinal anaesthesia was discovered by August bier in 1898, one of the most common reason for failure of the procedure continues to be anxiety and fear from the patient which leads to failure of block and so, it is essential to adequately sedate the patient after administration of spinal anaesthesia. Most of the sedatives have problems like hypotension, bradycardia and also provides unreliable sedation, that is, the dose required for every patient may vary widely.

This study was formulated in such a way to address these two problems. Dexmedetomidine, a selective α 2 agonist produces arousable sedation, hypnosis, anxiolytic and antishivering properties. It can cause decrease in heart rate and blood pressure. Tramadol is a semi synthetic opioid which controls shivering and also sedation. It has a high incidence of vomiting and in various studies, it is found to be approximately 70% [7]. So, all the patients in our study were given Inj.Ondansetron 4mg I.V. irrespective of the study group. Pethidine is a synthetic opioid which is a time tested gold standard drug used for the control of shivering. Pethidine also causes sedation.

Various studies have been conducted to study these drugs in the control of shivering. Many studies were conducted in patients who underwent general anaesthesia. The number of studies conducted after spinal anaesthesia are relatively less. Various studies were conducted after the onset of shivering for its treatment. We planned a study to find out the efficiency of these drugs in the prevention of shivering. Our study was

planned in a prospective, randomized double blind manner to study the efficacy of these three drugs in the prevention of shivering. The study was double blinded wherein the patient and observer were blinded. In our study the sample size was calculated as **90** based on previous studies to obtain results of the study with a power of 90% and a significance level of 0.05.

Patients between the age of 18 and 65 were selected as the paediatric patients are not suitable for spinal anaesthesia and the geriatric patients will have age related changes which can confound the variables. On analysing the demographic profile, the distribution of age, sex and height of the patients in both the groups are comparable.

Shivering

The primary outcome measure studied was the ability of the drugs in the prevention of shivering among the study population. Among the three drugs used in the study, dexmedetomidine was found to be superior to other drugs in the prevention of shivering as only one patient among the 30 patients who were given dexmedetomidine had shivering. This result is in accordance with the report by **Lim fern et al** [43] study which also had a similar outcome. Tramadol group patients had the highest incidence of shivering with 12 patients in that group had shivering grade >2. Pethidine group had a response rate between the two and 3 patients had shivering grade >2. This result is a bit of change when compared to **Lim fern et al** [43] as in both tramadol and pethidine group

there was similar response but was a statistically poor outcome for both groups when compared with dexmedetomidine group. The reason for this difference could have been because that study was given to patients after the patients shivered as for treatment. When compared with **Mittal et al [44]** study, which was a 2 drug comparison between dexmedetomidine and tramadol, showed that both drugs were equally effective but dexmedetomidine had a faster onset of action. Again, it was an intraoperative study where drugs were given after the onset of shivering. In **Bozgeyik et al [45]** dexmedetomidine and tramadol were given along with a placebo element, both drugs were equally efficient in the prevention of shivering. The tramadol dose used in this study was 100 mg in all patients which could have been the cause for variation in the results. The results in **Philip et al [48]** study was tramadol and pethidine were equally effective but tramadol had a faster onset of action but tramadol was administered at a dosage of 1 mg/kg in this study. In our study, the need for rescue drug was higher in tramadol group when compared with other two drugs. This might have been different if tramadol was used at a dosage of 1mg/kg or higher.

Sedation

The secondary outcome measure of the study was sedation. All the drugs used in the study for prevention of shivering can cause sedation to varying degrees. So no other sedatives or hypnotics or anxiolytics

were given during the study. Undoubtedly, dexmedetomidine stood far superior to the other two drugs. The onset of sedation was almost 5 minutes and had a sedation score of 3 (Drowsy, arousable to physical stimuli) in most of the patients. Sedation after the bolus dose lasted for over 90 minutes and patients were comfortable during the surgery. In tramadol group, only 40% of the patients were sedated and the sedation scale was also 2. The onset of sedation was also slower and was around 15 minutes. Pethidine had a sedation scale better than tramadol but was still far below dexmedetomidine group. This observation was similar in other studies also. **Mittal et al [44]** concluded the study as sedation due to dexmedetomidine provides additional comfort to the patient. **Bozgeyik et al [45]** had a similar observation as dexmedetomidine causes sedation and relieves anxiety. **Usta B et al [41]** study also, sedation scores were higher in dexmedetomidine group and was convincing for the patient. The sedation caused by dexmedetomidine causes the patient to be in a tranquil state but follows oral commands as seen in **Elvan et al [54].** The sedation score was higher in dexmedetomidine group starting from 5 minutes as observed in **Bozgeyik et al [45]** is the similar result in our study too.

Side effects

In dexmedetomidine group, 3 patients had bradycardia out of 30 patients while in other two groups, no episodes of bradycardia was noted. In dexmedetomidine group, 2 patients had hypotension out of 30 patients

while in other two groups, no episodes of hypotension occurred. These events were not statistically significant and were promptly treated. No patient in any group had respiratory depression. Hypotension and bradycardia are known hemodynamic effects of dexmedetomidine but only few patients have those side effects which is acceptable as concluded by **Lim fern et al [43]**. Hypotension and bradycardia were seen in dexmedetomidine group but is of lesser incidence as concluded by **Usta B et al[41]** was the similar observation in our study also. No other adverse outcomes like nausea, vomiting, headache, respiratory depression etc., noted in any of the groups. The axillary temperatures measured between the groups were comparable and no significant differences was found.

There are limitations in any study and in our study, different doses of dexmedetomidine and difference between use as infusions and bolus doses are to be evaluated for preventing shivering as to which is ideal with minimum haemodynamic adverse effects, which needs further studies. The dose of tramadol used for the study at 0.5mg/kg proved to be insufficient and higher doses of tramadol at 1mg/kg may be needed to prevent shivering and further studies on different dosing of the drug in similar conditions will help in sorting out the same.

CHAPTER 08

CONCLUSION

- Dexmedetomidine is more effective in the prevention of shivering when compared with pethidine and tramadol.
- Dexmedetomidine has an added advantage of adequate reliable sedation.
- Pethidine is also equally effective in the prevention of shivering and is more efficient than tramadol.

Hence we conclude that Dexmedetomidine at 0.5µg/kg is most effective in the prevention of shivering when compared with pethidine and tramadol.

BIBLIOGRAPHY

1. De Witte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. Anesthesiology 2002;96:467-84.
2. Buggy DJ, Crossley AW. Thermoregulation, mild perioperative hypothermia and postanesthetic shivering. Br J Anaesth 2000;84:615-28.
3. Shreyavathi R, A. K. Kavitha, Raghavendra Rao R. S, Bhaskara B. Comparison of Intravenous Ketamine, Clonidine or Dexmedetomidine Prior to Subarachnoid Blockade for Control of Shivering. Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 45, September 18; Page: 1102111027, DOI: 10.14260/jemds/2014/3438.
4. Glosten B, Sessler DI, Faure EA, Karl L, Thisted RA. Central temperature changes are poorly perceived during epidural anesthesia. Anesthesiology. 1992;77:10-6, doi: 10.1097/00000542-199207000-00003.
5. Ozaki M, Kurz A, Sessler DI, Lenhardt R, Schroeder M, Moayeri A, Noyes KM, Rotheneder E. Thermoregulatory thresholds during epidural and spinal anesthesia. Anesthesiology. 1994;8:282:8, doi: 10.1097/ 00000542-199408000-00004.
6. Katyal S, Tewari A. Shivering: Anaesthetic considerations. J AnaesthClinPharmacol 2002;18:363-76.

7. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth 2011;55:242-6.
8. Reddy VS, Chiruvella S. Clonidine versus tramadol for post spinal shivering during caesarean section: A randomized double blind clinical study. J ObstetAnaesthCrit Care 2011;1:26-9.
9. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anaesthesia. Anesthesiology 74:581-605, 1991
10. Brauchi S, Orta G, Salazar M, et al: A hotsensing cold receptor: C-terminal domain determines thermosensation in transient receptor potential channels. J Neurosci 26:4835-4840, 2006.
11. Poulos DA: Central processing of cutaneous temperature information. Fed Proc 40:2825-2829, 1981.
12. Jessen C, Feistkorn G: Some characteristics of core temperature signals in the conscious goat. Am J Physiol 247:R456-R464, 1984.
13. Simon E: Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev PhysiolBiochemPharmacol 71:1-76, 1974.
14. Vassilieff N, Rosencher N, Sessler DI, Conseiller C: The shivering threshold during spinal anesthesia is reduced in the elderly. Anesthesiology 83:1162-1166, 1995.
15. Cheng C, Matsukawa T, Sessler DI, et al: Increasing mean skin temperature linearly reduces the coretemperature thresholds for vasoconstriction and shivering in humans. Anesthesiology 82:1160-1168, 1995.

16. Hales JRS: Skin arteriovenous anastomoses, their control and role in thermoregulation. *In* Johansen K, Burggren W (eds): Cardiovascular Shunts: Phylogenetic, Ontogenetic and Clinical Aspects. Copenhagen, Munksgaard, 1985, pp 433-451.
17. Hemingway A, Price WM: The autonomic nervous system and regulation of body temperature. Anesthesiology 29:693-701, 1968.
18. Kurz A, Sessler DI, Schroeder M, Kurz M: Thermoregulatory response thresholds during spinal anesthesia. AnesthAnalg 77:721-726, 1993.
19. Rajek A, Greif R, Sessler DI: Effects of epidural anesthesia on thermal sensation. RegAnesth Pain Med 26:527-531, 2001.
20. Leslie K, Sessler DI: Reduction in the shivering threshold is proportional to spinal block height. Anesthesiology 84:1327-1331, 1996.
21. Matsukawa T, Kurz A, Sessler DI, et al: Propofol linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 82:1169-1180, 1995.
22. *Giesbrecht GG, Sessler DI, Mekjavic IB, Schroeder M, Bristow GW*. Treatment of immersion hypothermia by direct body-tobody contact, J ApplPhysiol 1994; 76: 2373-2379.
23. Soliman MG, Gillies DMM: Muscular hyperactivity after general anaesthesia. Can AnaesthSoc J 19:529- 535, 1972.
24. Rosenberg H, Clofine R, Bialik O: Neurologic changes during awakening from anesthesia. Anesthesiology 54:125-130, 1981.
25. Imamura M, Matsukawa T, Ozaki M, et al: The accuracy and precision of four infrared aural canal thermometers during cardiac surgery. ActaAnaesthesiolScand 42:1222-1226, 1998.

26. *Sessler DI, Schroeder M*. Heat loss in humans covered with cotton hospital blankets, AnesthAnalg 1993; 77: 73-77.
27. *Kurz A, Kurz M, Poeschl G, Faryniak B, Redl G, Hackl W*. Forced-air warming maintains intraoperative normothermia better than circulating-water mattresses. AnesthAnalg 1993; 77: 89-95.
28. CodinaJ,Yatani A, Grenet D, Brown AM, Birnbaumer L. The alpha subunit of the GTP binding protein GK opens atrial potassium channels. Science. 1987; 236(4800): 442-5.
29. Unnerstall JR, Kopajtic TA, Kuhar MJ. Distribution of alpha 2 agonist binding sites in the rat and human central nervous system :analysis of some functional, anatomic correlates of the pharmacologic effects of Clonidine and related adrenergic agents. Brain Res. 1984; 319(1): 69-101.
30. Kamibayashi T, Maze M. Clinical uses of alpha 2 adrenergic agonists. Anesthesiology. 2000;93(5): 1345-9.
31. Davies MF, Haimor F, Lighthall G, Clark JD: Dexmedetomidine fails to cause hyperalgesia after cessation of chronic administration. AnesthAnalg 96:195-200, 2003.
32. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of Dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. British Journal of Anaesthesia. 2002; 88(5): 669-75.
33. Panzer O, Moitra V, Sladen RN. Pharmacology of sedative –analgesic agents: Dexmedetomidine, Remifentanil, Ketamine, volatile anaesthetics, and the role of peripheral mu agonists. AnesthesiologyClin. 2011;29:587-605

34. Aho M, Erkola O, Kallio A, et al: Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J ClinAnesth 5:194-203, 1993
35. Asano T, Dohi S, Ohta S, et al: Antinociception by epidural and systemic alpha(2)-adrenoceptor agonists and their binding affinity in rat spinal cordand brain. AnesthAnalg 90:400-407, 2000
36. Yung-Wei H, Robertson K, Young C, et al: Compare the respiratory effectsof remifentanil and dexmedetomidine.Anesthesiology 95:A1357, 2001.
37. Triltsch AE, Welte M, von Homeyer P, et al: Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. CritCareMed 30:1007-1014, 2002.
38. Aantaa R, Kanto J, Scheinin M, et al: Dexmedetomidine, an alpha 2- adrenoceptor agonist, reduces anaesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology 73:230- 235, 1990.
39. Aho M, Lehtinen AM, Erkola O, et al: The effect of intravenouslyadministered dexmedetomidine on perioperative hemodynamics andisoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology 74:997-1002, 1991.
40. Bajwa SJ, Gupta S, Kaur J, Singh A, Parmar S. Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study. J AnaesthesiolClinPharmacol 2012;28:86-91.
41. Usta B, Gozdemir M, Demircioglu RI, Muslu B, Sert H, Yaldiz A. Dexmedetomidine for the prevention of shiveringduring spinal anesthesia. Clinics (Sao Paulo) 2011;66:1187-91.

42. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, *et al*.Dexmedetomidine and clonidine in epidural anaesthesia:A comparative evaluation. Indian J Anaesth 2011;55:116-21.
43. Lim Fern[a] and Karis Misiran[b].Comparison of dexmedetomidine, pethidine and tramadol in the treatment ofpost-neuraxial anaesthesia shivering.Southern African Journal of Anaesthesia and Analgesia 2015;21 (1) : 21-26.
44. Mittal G, Gupta K, Katyal S, Kaushal S. Randomised double-blind comparative study of dexmedetomidine and tramadolfor post-spinal anaesthesia shivering. Indian J Anaesth 2014;58:257-62.
45. Semsettin Bozgeyik1, AyseMizrak, ErtuğrulKılıç, FatihYendi,Berna Kaya Ugur et al.The Effects of Preemptive Tramadol and Dexmedetomidine on Shivering During Arthroscopy.Vol. 8, Issue 2, April-June 2014.
46. Yong-Shin Kim1, Yong-Il Kim2, Kwon-Hui Seo1, Hye-Rim Kang1 et al. Optimal Dose of Prophylactic Dexmedetomidine for Preventing Postoperative Shivering. International Journal of Medical Sciences2013; 10(10):1327-1332. doi: 10.7150/ijms.6531
47. M. Mohta,1 N. Kumari,2 A. Tyagi,1 A. K. Sethi,3 D. Agarwal4 and M. Singh4 et al. Tramadol for prevention of postanaesthetic shivering:a randomised double-blind comparison with pethidine. Journal of the association of the anaesthetists of great Britain and Ireland.Anaesthesia, 2009, 64, pages 141–146.
48. Philip, *et al.:* Antishivering Effect of Tramadol and Pethidine.International Journal of Scientific Study | September 2014 | Vol 2 | Issue 6.

49. Dr. Aditi A. Dhimar1 Dr. Mamta G. Patel2 Dr. (Mrs.) V. N. Swadia3 et al.TRAMADOL FOR CONTROL OF SHIVERING(COMPARISON WITH PETHIDINE). Indian J. Anaesth. 2007; 51 (1) : 28 – 31.
50. Anurag Tewari, Ira Dhawan, VidhiMahendru, Sunil Katyal,Avtar Singh, Shuchita Garg et al. Use of oral tramadol to prevent perianestheticshivering in patients undergoing transurethral resection of prostate under subarachnoid blockade. Vol. 8, Issue 1, January-March 2014.
51. Yeon. A .kim, Tae dong kweon et al. comparison of meperidine and Nefopam for prevention of shivering during spinal anaesthesia. Korean J Anesthesio. 2013 Mar;64(3):229-233.
52. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethidine and doxapramin the treatment of post-anaesthetic shivering. Anaesthesia 1997;52:32-6.
53. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A doseresponsestudy. Anesthesiology 1994;81:591-601.
54. Elvan EG, Qc B, Uzun S et al. Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. Eur JAnaesthesiol 2008; 25: 357-64.

ANNEXURES

Ethical committee approval letter

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study of dexmeditomidine, tramadol and pethidine in the preventive of intraoperative shivering in patients undergoing surgery under spinal anesthesia.

Principal Investigator : Dr. Azhagappan . C

Designation : PG MD (Anesthesiology)

Department : Department of Anesthesiology
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.02.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

PROFORMA

DATE

NAME : AGE/SEX :

SERIAL NO :

I.P. NO : ADDRESS :

WEIGHT : HEIGHT : BMI :

DIAGNOSIS : PROCEDURE :

ASA GRADE GROUP :

H/O OTHER MEDICAL/SURGICAL ILLNESS

DRUG H/O

ALLERGIC H/O

ON EXAMINATION Anemia/Icterus/Cyanosis/Clubbing/Pedal Edema

Pulse rate /min Blood Pressure mmHg SpO2

Cardiovascular system

Respiratory System

INVESTIGATIONS

Hb g% MPC

BT Dentition

CT Neck

RBS Back

Blood Urea

Serum Creatinine

ECG Chest X-Ray

OTHERS

Monitors : Pulse oximetry/ Non-invasive Blood Pressure/ ECG

IV access with 18 gauge cannula

IV fluids (RL at 10ml/kg)

Subarachnoid block will be performed

Study drug will be infused over 10 min

TIME	HEART RATE	BLOOD PRESSURE	SpO_2	SHIVERING GRADE	SEDATION SCALE	Temperature
Baseline						
5						
10						
15						
30						
45						
60						
75						
90						
105						
120						

Additional Drugs given :

□ந□ய□கி தகவல் த□ள்

□□□தண்□ மயக்க ம□ந்□ □ழ் அதி□வ சி□ச்□ச□ன் □ப□□ உடல் ந□க்கம் த□க்க Dexmeditomidine, Tramadol, □பத்□□ன் ஒப்பிட்□ ஆய்□

ஆர□ய்ச்சி□ ன் □ந□க்க□ம் ஆத□ரங்க□ ம் :

அதி□வ சி□ச்□ச□ன் □ப□□ பல □ந□ய□கி க□ க்□ உடல் ந□க்கம் ஏற்ப□வதற்க□ன வ□ய்ப்□கள் அ□கம். இத□ன கட்□ப்ப□த்□வதற்க□க Tramadol, □பத்□□ன் ஆ□ய இரண்□ ம□ந்□க□ ம் பயன்ப□த்தப்ப□□ற□. Dexmeditomidine என்□ற ம□ந்□ அண்□மக□லமக உப□ய□கப்ப□த்தப்ப□□ற□. இந்த ம□ந்□ உடல் ந□க்கத்□த நன்ற□க கட்□ப்ப□த்□வத□க ஆய்□கள் உள்ளன. என□வ இந்த □ன்தி ம□ந்□க□ளா ம் ஒப்பிட்□ ப□ர்க்க இந்த ஆய்□ □மற்□க□ள்ளப்ப□□ற□.

ஆய்□ □□ற :

என□ ஆர□ய்ச்சி□ல் □ங்கள் ந□ன்□ □□வ□க பி□க்கப்ப□□ர்கள். ழிதல□ம் □□நி ற்□ Dexmeditomidine, இரண்ட□ம் □□நி ற்□ Tramadol, □ன்ற□ம் □□நி ற்□ □பத்□□ன், ந□ன்க□ம் □□நி ற்□ ந□ர்மல் ச□லன் வழங்கப்ப□ம். தங்க□ க்□ ந□க்கம் ஏற்ப□□றத□ என்தி 2 ம□ □நரம் கண்க□□ க்கப்ப□ம்.

உண்ட□கக்□ □ய இட□ர்கள் :

இந்த ஆய்நி ல் பயன்ப□த்தப்ப□ம் ம□ந்□கள□ல் தங்க□ க்□ □மட்டல், வ□ந்□, மயக்கம் ஏற்பட வ□ய்ப்□ள்ள□.

ஆய்□ல் உங்கள் உ□□மகள் :

உங்கள் ம□த்□வ ப□□வ□கள் அந்தரங்கம□க □வக்கப்ப□ம். இந்த ஆய்நி ன் ழி□□கள் பத்□□க்□ககி ல் □வகி □டப்படல□ம். ஆன□ல் உங்கள் □பயர் அ□டய□ளம் க□ட்டப்பட□□. இந்த ஆய்நி ல் பங்□கற்ப□ தன்□ ச்□சய□ன□ மற்தி ம் □வதி க□ரணங்கள□ல் □ங்கள் எத□ம் □ற□ம□ல□ய எப்□ப□□ □வண்□□மன்ற□□ ம் நி ல□க்□க□ள்ளல□ம். ஏ□த□ ம் பக்கநி □ள□கள் ஏற்பட்ட□ல் ழி□ சி□ச்□சா ம் ம□த்□வக் □□நி னர□ல் உடன□ய□க வழங்கப்ப□ம்.

ந□ள் :

□ந□ய□கி □ன் □க□ய□ப்பம்
(இட□ □ப□நி ரல் □ர□க)
ம□த்□வர□ல் ப□த்□க் க□ட்டப்பட்ட□.

□ய ஒப்□தல் ப□வம்

□□□தண்□ மயக்க ம□ந்□ □ழ் அதி□வ சி□ச்□ச□ன் □ப□□ உடல் ந□க்கம் த□க்க Dexmeditomidine, Tramadol, □பத்□□ன் ஒப்பிட்□ ஆய்□

ஆய்வ□ளர் : **ம□. □ச.அழகப்பன்**
ழி□ரி□ல பட்ட□மற்ப□ப்□ ம□ணவர்
மயக்கநி யல் □□ற.

வ□க□ட்□ : **□பர□சி□யர் ம□.□□ஷ்ண□ம□ர்**
மயக்கநி யல் □□ற
அர□ ஸ்ட□ன்□ ம□த்□வம□ன.

□பயர் வய□ உள்கி □ப்□ எண். :

இந்த ம□த்□வ ஆய்நி ன் நி வரங்கள் எனக்□ நி ளக்கப்பட்ட□. என்□ □டய சந்□தகங்க□ள □ர்க்க□ம் அதற்க□ன தெ□ந்த நி ளக்கங்க□ள □பற□ம் வ□ய்ப்பகி க்கப்பட்ட□.

ந□ன் இவ்வ□ய்நி ல் தன்□ ச்□சய□கத□ன் பங்□கற்□□றன். எந்த க□ரணத்□ன□□ம் எந்த கட்டத்□□ம் எந்த சட்டசிக்க□ம் இன்றி இந்த ஆய்நி □□ந்□ நி ல□க் □க□ள்ளல□ம் என்தி ம் அறிந்□ □க□ண்ட□ன்.

ந□ன் ஆய்நி □□ந்□ நி ல□க் □க□ண்ட□□ம் ஆய்வ□ளர் என்□ □டய ம□த்□வ அறிக்□கக□ள ப□ர்ப்பதற்□க□ அல்ல□ உப□ய□□க்க□வ□ என் அ□ ம□ □த□வ□ல்□ல எனம் அறிந்□ □க□ண்ட□ன். என்□ன பற்றிய தகவல்கள் ரகசியம□க ப□□க□க்கப்ப□ம் என்ப□தா ம் அறி□வன்.

இந்த ஆய்நி ன் □ லம் □□ டக்□ம் தகவல்க□ளா ம் ப□□ச□த□ன ழி□□க□ளா ம் ஆய்வ□ளர் அவர் நி □ப்பத்□ற்□கற்ப பயன்ப□த்□க் □க□ள்ள□ம் அத□ன பிர□□க்க□ம் ழி□மன□டன் சம்ம□க்□□றன்.

இந்த ஆய்நி ல் பங்□ □க□ள்ள ஒப்□க்□க□ள்□□றன். எனக்□ □க□□க்கப்பட்□ள்ள அறி□□ரகசி ன்ப□ நடந்□ □க□ள்வ□டன் ஆய்வ□ள□க்□ உண்□மா டன் இ□ப்□பன், என்□ ம் உதி □ அசி க்□□றன்.

உடல்நலம் ப□□க்கப்பட்ட□□ல□ வழக்கத்□ற்□ ம□ற□ன □நய்□றி □தன்பட்ட□□ல□ அத□ன □த□நி ப்□பன் என்தி உதி □ □தி□□றன்.

இந்த ஆய்நி ல் எனக்□ எவ்நி தம□ன ப□□ச□த□னக□ளா ம் சி□ச்□சக□ளா ம் □மற்□க□ள்ள ந□ன் ழி□மன□டன் சம்ம□க்□□றன்.

இப்ப□க்□

□நய□சி □ன் □க□ய□ப்பம் ஆய்வ□ள□ன் □க□ய□ப்பம்

(□பயர்)

NAME	AGE	SEX	DATE	Height	Weight	DIAGNOSIS
NAVEEN	46	M	18.05.2015	1.68	66	ING HERNIA
SEKAR	45	M	18.05.2015	1.72	72	VARICOSE.V
SASIKALA	34	F	18.05.2015	1.55	62	INCISIONAL HERNIA
MURALI	38	M	19.05.2015	1.61	70	HYDROCELE
KOTHANDAM	55	M	19.05.2015	1.74	75	ING HERNIA
SURESH	35	M	20.05.2015	1.58	62	HYDROCELE
KRISHNAVENI	30	F	20.05.2015	1.51	65	PTRA R LEG
VIJAYA	40	F	20.05.2015	1.62	70	PTRA R LEG
KRISHNA	47	M	20.05.2015	1.74	72	ING HERNIA
SRINI	29	M	21.05.2015	1.58	65	VARICOCELE
JAYAPRAKASH	35	M	21.05.2015	1.72	80	VARICOSE.V
GOPI	32	M	22.05.2015	1.64	70	PTRA R LEG
KAMSALA	36	F	22.05.2015	1.56	52	VARICOSE.V
JAMBU	44	M	23.05.2015	1.6	77	HYDROCELE
GURUMOORTHY	60	M	23.05.2015	1.62	61	ING HERNIA
DHARMARAJ	29	M	26.05.2015	1.68	56	ING HERNIA
KUMAR	44	M	26.05.2015	1.52	59	ING HERNIA
SRINIVASAN	54	M	28.05.2015	1.61	51	HYDROCELE
VELU	31	M	28.05.2015	1.72	80	VARICOSE.V
DHANALAXMI	45	F	29.05.2015	1.52	56	INCISIONAL HERNIA
PANNERSELVAM	47	M	16.06.2015	1.75	85	ING HERNIA
GOVINDASAMY	52	M	16.06.2015	1.66	62	HYDROCELE
MOHAN	23	M	16.06.2015	1.82	77	PTRA R LEG
RAJA	35	M	16.06.2015	1.48	52	HYDROCELE
GNANASEKAR	33	M	16.06.2015	1.68	74	VARICOSE V
LATHA	30	M	18.06.2015	1.7	71	VARICOSE V
SIVASANKAR	44	M	18.06.2015	1.65	60	PTRA R LEG
RAJA	28	M	19.06.2015	1.58	51	ING HERNIA
JEGANNATHAN	30	M	19.06.2015	1.7	68	ING HERNIA
RAJESH	32	M	19.06.2015	1.66	62	HYDROCELE
ABBAS	46	M	19.06.2015	1.71	78	ING HERNIA
SARADHA	34	F	22.06.2015	1.62	68	VARICOSE V
SUBRAMANI	58	M	22.06.2015	1.67	65	HYDROCELE
SUBBIAH	58	M	22.06.2015	1.62	66	VARICOSE V
KAVIARASU	29	M	22.06.2015	1.68	61	ING HERNIA
KOTHANDAM	52	M	23.06.2015	1.72	65	VARICOSE V
KRISHNAN	45	M	23.06.2015	1.52	56	PTRA R LEG
MOHAN	34	M	23.06.2015	1.61	70	ING HERNIA
BASHA	30	M	25.06.2015	1.74	84	ING HERNIA
ESHWARAN	50	M	28.06.2015	1.66	62	PTRA R LEG
GOVINDARAJ	44	M	28.06.2015	1.74	78	ING HERNIA
MADHAVAN	31	M	28.06.2015	1.58	52	HYDROCELE
RAJAM	45	F	28.06.2015	1.66	71	VARICOSE V
SINGARAVEL	47	M	29.06.2015	1.75	80	ING HERNIA
SELVARAJ	51	M	29.06.2015	1.62	65	ING HERNIA

RAJI	32	M	29.06.2015	1.71	68	ING HERNIA
ARAVIND	49	M	29.06.2015	1.58	51	VARICOSE V
VELAYUTHAM	48	M	01.07.2015	1.65	55	ING HERNIA
REVATHY	26	F	01.07.2015	1.68	75	PTRA R LEG
GOVINDAMMAL	45	F	01.07.2015	1.56	51	VARICOSE V
SHANKAR	58	M	02.07.2015	1.61	65	ING HERNIA
VENKATESAN	45	M	02.07.2015	1.72	74	PTRA R LEG
BABU	41	M	02.07.2015	1.58	62	ING HERNIA
FATHIMA	32	F	02.07.2015	1.62	62	PTRA R LEG
CHINNADURAI	38	M	02.07.2015	1.72	66	ING HERNIA
VIGNESH	23	M	05.07.2015	1.82	85	VARICOSE V
HUSSAIN	41	M	05.07.2015	1.57	60	VARICOSE V
JAISHANKAR	44	M	05.07.2015	1.71	64	ING HERNIA
MURUGAN	33	M	05.07.2015	1.73	74	ING HERNIA
ELUMALAI	32	M	05.07.2015	1.56	69	ING HERNIA
MOSES	51	M	06.07.2015	1.68	74	ING HERNIA
DURAI	44	M	06.07.2015	1.74	80	HYDROCELE
RAM	23	M	07.07.2015	1.66	71	HYDROCELE
SURESH	52	M	07.07.2015	1.56	53	PTRA R LEG
RAMESH	37	M	07.07.2015	1.72	80	ING HERNIA
ANBU	44	F	08.07.2015	1.61	68	VARICOSE V
ARUN	51	M	08.07.2015	1.77	84	ING HERNIA
PADMAVATHY	39	F	09.07.2015	1.51	53	PTRA R LEG
SUNDARRAJ	45	M	09.07.2015	1.66	70	ING HERNIA
VEERAN	51	M	09.07.2015	1.7	67	VARICOSE V
BALAJI	22	M	12.07.2015	1.68	65	HYDROCELE
MICHAEL	56	M	12.07.2015	1.55	51	ING HERNIA
SOORIYA	42	M	13.07.2015	1.66	75	ING HERNIA
VENKATESAN	53	M	13.07.2015	1.58	55	VARICOSE V
PRABAKAR	31	M	14.07.2015	1.65	70	HYDROCELE
KAMATCHI	42	F	14.07.2015	1.55	52	PTRA R LEG
SUNDER	52	M	15.07.2015	1.61	65	VARICOSE V
NAGARAJ	44	M	15.07.2015	1.52	60	HYDROCELE
PRAKASH	23	M	15.07.2015	1.62	71	HYDROCELE
DEEPAN	32	M	16.07.2015	1.71	75	ING HERNIA
DINESH	32	M	16.07.2015	1.74	82	VARICOSE V
DEEPA	26	F	16.07.2015	1.52	60	PTRA R LEG
ANTONY	45	M	19.07.2015	1.66	53	ING HERNIA
SHRUTI	42	F	20.07.2015	1.58	60	VARICOSE V
MAHESH	34	M	20.07.2015	1.71	68	ING HERNIA
HARISH	21	M	20.07.2015	1.69	58	HYDROCELE
MOHAN RAM	38	M	21.07.2015	1.77	82	ING HERNIA
ANJALAI	52	F	21.07.2015	1.56	62	VARICOSE V
SARANYA	33	F	21.07.2015	1.6	65	PTRA R LEG
MUTHU	23	M	21.07.2015	1.62	58	HYDROCELE

PROCEDURE	ASA	GROUP	Shivering (mins)									
			0	5	10	15	30	45	60	75	90	105
HERNIOPLASTY	1	T	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	3	0	0
MESH REPAIR	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	2	D	0	0	0	0	0	0	0	0	0	0
SSG	1	T	0	0	0	3	0	0	0	0	0	0
SSG	1	D	0	0	0	0	1	3	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	1	3	0	0	0	0
VARICOCELECTOMY	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
SSG	2	D	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	T	0	0	0	2	3	0	0	0	0	0
EVERSION OF SAC	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	3	0	0	0	0	0	0
EVERSION OF SAC	2	D	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	D	0	0	0	0	0	0	0	0	0	0
MESH REPAIR	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	3	0	0	0	0	0
EVERSION OF SAC	2	T	0	0	0	0	0	0	0	0	0	0
SSG	1	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	2	3	0	0	0	0	0
TRENDELENBURG	1	D	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	3	0	0	0	0	0
SSG	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	2	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	2	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	1	2	1	1	0	0
TRENDELENBURG	2	P	0	0	0	0	0	0	0	0	0	0
SSG	2	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	0	0	0	0	0	0
SSG	2	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	P	0	0	0	0	0	0	0	0	0	0

HERNIOPLASTY	2	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	3	0	0	0	0	0
HERNIOPLASTY	2	T	0	0	0	0	0	0	0	0	0	0
SSG	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	2	T	0	0	0	1	3	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
SSG	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
SSG	1	T	0	0	0	0	1	3	0	0	0	0
HERNIOPLASTY	2	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	T	0	0	0	0	3	0	0	0	0	0
EVERSION OF SAC	1	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	0	0	0	0	0	0	0
SSG	2	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
SSG	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	0	0	0	0	0	0	0
SSG	1	T	0	0	0	0	3	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	D	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	1	T	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	P	0	0	0	0	0	0	0	0	0	0
SSG	1	T	0	0	0	2	3	0	0	0	0	0
HERNIOPLASTY	1	P	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	T	0	0	0	0	0	0	0	0	0	0
HERNIOPLASTY	2	P	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	T	0	0	0	0	3	0	0	0	0	0
HERNIOPLASTY	1	D	0	0	0	0	0	0	0	0	0	0
TRENDELENBURG	1	T	0	0	0	0	0	0	0	0	0	0
SSG	1	D	0	0	0	0	0	0	0	0	0	0
EVERSION OF SAC	1	P	0	0	0	0	0	0	0	0	0	0

	Sedation (mins)													
120	0	5	10	15	30	45	60	75	90	105	120	Rescue	0	5
0	1	1	1	1	1	1	1	1	1	1	1	N	84	80
0	1	1	1	2	2	2	1	1	1	1	1	Y	87	85
0	1	1	1	3	3	3	3	2	2	2	1	N	96	92
0	1	1	1	1	2	2	1	1	1	1	1	N	98	90
0	1	1	1	3	3	3	3	2	2	2	1	N	91	91
0	1	1	1	3	3	3	3	3	3	2	1	N	88	86
0	1	1	1	1	1	2	2	1	1	1	1	Y	90	80
0	1	1	1	2	2	2	2	1	1	1	1	Y	98	84
0	1	1	1	1	1	1	2	1	1	1	1	Y	80	76
0	1	1	1	2	2	2	2	2	1	1	1	N	84	85
1	1	1	1	1	1	1	1	1	1	1	1	N	61	65
0	1	1	1	3	3	3	3	2	2	2	1	N	94	90
0	1	1	1	1	1	1	2	2	2	1	1	Y	93	90
0	1	1	1	3	3	3	3	2	2	2	1	N	97	88
0	1	1	1	1	1	1	1	1	1	1	1	N	68	64
0	1	1	1	3	3	3	2	2	2	1	1	N	82	75
0	1	1	1	1	2	2	2	1	1	1	1	Y	66	62
0	1	1	1	3	3	3	3	3	2	2	1	N	78	74
0	1	1	1	3	3	3	2	2	1	1	1	N	98	90
0	1	1	1	1	1	1	1	1	1	1	1	N	85	80
0	1	1	1	1	1	1	2	2	2	1	1	Y	95	91
0	1	1	1	1	1	1	1	1	1	1	1	N	96	92
0	1	1	1	2	2	1	1	1	1	1	1	N	86	82
0	1	1	1	1	2	2	1	1	1	1	1	Y	88	84
0	1	1	1	2	3	3	2	2	2	2	1	N	86	80
0	1	1	1	1	2	2	2	2	2	1	1	Y	78	72
0	1	1	1	2	2	2	1	1	1	1	1	N	90	84
0	1	1	1	3	3	3	3	2	2	1	1	N	88	86
0	1	1	1	3	3	3	3	2	2	2	1	N	74	78
0	1	1	1	1	2	2	2	2	1	1	1	N	78	82
0	1	1	1	2	2	2	2	2	1	1	1	N	84	86
0	1	1	1	3	3	3	3	2	2	2	1	N	82	80
0	1	1	1	2	2	2	1	1	1	1	1	N	88	90
0	1	1	1	2	2	2	2	2	2	1	1	N	86	85
0	1	1	1	1	2	2	1	1	1	1	1	N	78	77
0	1	1	1	2	2	2	1	1	1	1	1	N	60	62
0	1	1	1	1	1	1	1	1	1	1	1	N	75	72
0	1	1	1	1	1	1	1	1	1	1	1	N	74	80
0	1	1	1	2	2	2	2	2	2	1	1	N	96	92
0	1	1	1	1	2	2	1	1	1	1	1	N	62	60
0	1	1	1	1	1	1	1	1	1	1	1	N	77	74
0	1	1	1	1	1	1	1	1	1	1	1	N	92	90
0	1	1	1	1	2	2	2	2	1	1	1	N	70	75
0	1	1	1	1	1	1	1	1	1	1	1	N	68	72
0	1	1	1	2	2	2	2	1	1	1	1	N	98	95

0	1	1	1	1	1	1	1	1	1	1	1	N	78	75
0	1	1	1	1	2	2	2	2	2	1	1	Y	64	63
0	1	1	1	2	2	2	1	1	1	1	1	N	95	92
0	1	1	1	1	1	1	1	1	1	1	1	N	88	86
0	1	1	1	1	2	2	2	2	2	1	1	Y	96	92
0	1	1	1	3	3	3	2	2	2	1	1	N	94	96
0	1	1	1	2	2	2	2	2	2	1	1	N	88	86
0	1	1	1	2	3	3	3	3	2	2	1	N	84	84
0	1	1	1	1	1	1	2	2	1	1	1	Y	80	78
0	1	1	1	2	2	2	2	1	1	1	1	N	95	96
0	1	1	1	3	3	3	3	2	1	1	1	N	90	92
0	1	1	1	3	3	3	3	2	2	1	1	N	72	75
0	1	1	1	2	2	2	2	2	2	1	1	N	74	78
0	1	1	1	1	2	2	1	1	1	1	1	N	68	66
0	1	1	1	3	3	3	3	3	2	1	1	N	88	85
0	1	1	1	1	2	2	2	2	1	1	1	Y	88	86
0	1	1	1	1	1	1	1	1	1	1	1	N	88	84
0	1	1	1	2	2	2	2	2	2	1	1	N	68	69
0	1	1	1	3	3	3	3	2	2	1	1	N	74	78
0	1	1	1	1	1	1	1	1	1	1	1	N	72	68
0	1	1	1	2	2	2	2	2	2	2	1	N	80	85
0	1	1	1	3	3	3	3	2	2	2	1	N	92	91
0	1	1	1	3	3	3	3	3	2	2	1	N	86	84
0	1	1	1	2	2	2	1	1	1	1	1	N	68	69
0	1	1	1	3	3	2	2	1	1	1	1	N	75	73
0	1	1	1	1	1	1	1	1	1	1	1	N	70	84
0	1	1	1	1	1	1	1	1	1	1	1	N	88	98
0	1	1	1	3	2	2	1	1	1	1	1	N	83	88
0	1	1	1	2	2	2	2	1	1	1	1	N	88	86
0	1	1	1	1	1	1	1	1	1	1	1	N	77	80
0	1	1	1	1	1	2	2	2	1	1	1	Y	92	85
0	1	1	1	2	2	2	2	2	1	1	1	N	86	74
0	1	1	1	1	1	1	1	1	1	1	1	N	80	75
0	1	1	1	3	3	3	2	2	1	1	1	N	75	80
0	1	1	1	1	1	1	1	1	1	1	1	N	87	82
0	1	1	1	2	2	2	2	2	2	1	1	N	88	86
0	1	1	1	1	3	2	2	2	2	1	1	Y	84	75
0	1	1	1	2	2	2	2	1	1	1	1	N	86	80
0	1	1	1	1	1	1	1	1	1	1	1	N	94	88
0	1	1	1	2	2	2	2	2	2	1	1	N	90	85
0	1	1	1	1	2	2	2	1	1	1	1	Y	78	84
0	1	1	1	3	3	3	3	2	2	1	1	N	66	68
0	1	1	1	2	2	1	1	1	1	1	1	N	82	82
0	1	1	1	3	3	3	2	2	2	2	1	N	80	85
0	1	1	1	2	2	2	2	2	2	1	1	N	85	86

Heart rate (min)									Systolic blood pressure (mm						
10	15	30	45	60	75	90	105	120	0	5	10	15	30	45	60
78	80	78	82	80	74	88	76	74	124	121	117	120	128	124	130
86	82	68	64	68	86	78	76	77	122	119	113	116	112	122	124
88	54	70	72	79	76	82	91	75	110	107	113	116	112	108	124
85	82	76	72	80	78	84	86	70	114	111	105	108	106	120	122
93	80	72	80	76	80	74	70	78	122	119	127	130	128	132	128
84	78	77	75	78	80	72	77	81	128	125	129	132	130	128	125
82	78	82	88	74	78	72	86	80	125	122	116	120	122	128	120
76	81	80	70	76	74	80	70	74	139	136	132	136	132	135	130
85	74	82	80	72	80	78	71	83	126	123	93	96	102	104	122
86	86	74	82	77	81	71	83	79	118	114	93	90	98	100	114
73	63	72	82	78	76	80	84	72	125	122	118	122	120	125	121
85	98	92	86	84	76	85	80	89	120	116	112	114	115	118	128
92	98	90	82	94	80	78	82	80	112	110	105	108	108	132	118
80	82	78	76	78	76	79	82	78	124	121	122	125	128	130	118
77	82	78	70	75	77	74	68	70	128	125	118	122	120	118	114
80	80	76	78	72	68	66	64	76	135	132	126	130	132	127	128
64	78	72	70	68	66	78	70	68	122	118	116	120	118	120	118
75	50	84	85	89	82	76	78	85	120	116	85	88	116	117	125
86	90	88	84	86	86	78	86	85	118	115	110	112	115	114	118
89	80	78	82	88	78	82	84	84	136	132	126	130	138	127	125
88	90	88	92	80	86	88	85	90	125	122	116	120	117	115	113
87	98	88	84	88	90	92	88	88	135	132	126	130	132	128	127
83	80	82	88	92	84	86	82	80	127	124	122	125	120	122	120
86	88	84	90	92	99	86	85	92	124	120	116	120	122	128	117
74	86	90	92	96	84	78	76	80	122	118	90	94	100	112	116
71	88	86	90	92	90	86	84	88	126	122	116	120	118	115	127
83	94	90	92	88	90	84	86	88	134	130	126	130	132	127	125
85	48	80	84	86	88	80	82	78	120	116	84	84	114	118	126
82	78	76	74	78	76	74	70	68	112	110	115	118	116	115	110
86	88	76	78	76	80	78	80	84	112	110	110	114	116	118	114
84	82	86	84	82	84	82	78	82	117	114	110	114	122	117	112
76	74	76	74	86	84	80	84	82	128	125	124	126	120	120	116
84	84	86	82	84	82	86	88	90	112	110	108	110	108	112	116
75	80	84	82	78	74	80	82	80	132	128	120	124	122	135	130
72	80	86	78	76	78	80	74	76	124	120	116	120	122	115	111
64	64	66	62	60	64	66	62	66	128	124	118	122	120	118	124
76	76	74	72	70	70	72	74	78	127	124	94	98	96	112	120
84	70	72	70	76	72	78	78	75	120	116	114	118	114	122	110
85	90	94	92	90	92	88	86	90	136	132	130	132	135	130	133
65	68	74	72	76	70	68	66	64	138	135	126	130	126	129	125
75	75	72	76	70	84	80	82	84	132	128	124	128	136	125	120
82	90	88	88	86	92	90	82	84	132	128	126	130	128	127	124
81	74	78	76	78	78	72	76	74	136	132	126	130	128	132	124
75	64	62	68	70	68	66	64	62	127	124	118	122	126	120	128
92	90	88	86	88	92	90	88	84	125	122	114	118	122	117	125

73	78	72	82	72	75	70	72	74	120	116	114	118	119	120	118
84	62	66	68	70	68	62	64	68	136	132	126	130	128	124	130
85	90	92	94	90	92	88	86	92	122	118	114	118	115	116	122
86	92	90	86	88	86	88	86	88	130	126	120	124	126	122	128
80	90	88	90	88	86	90	85	80	112	108	108	110	108	115	116
92	90	88	86	88	84	88	86	90	132	128	124	128	125	122	120
80	84	82	86	84	86	84	82	86	122	118	96	100	106	122	124
85	80	82	86	88	82	84	78	74	136	132	126	130	132	128	130
80	86	82	80	78	76	72	78	71	118	114	108	112	115	110	116
90	90	88	88	92	86	92	90	88	128	124	116	120	122	120	118
84	88	92	86	88	90	84	82	88	128	124	112	116	118	122	125
80	74	78	70	75	78	80	82	74	125	122	112	116	120	118	120
81	78	72	70	68	70	68	70	72	128	124	112	116	114	118	122
84	66	70	68	64	62	66	60	64	138	134	126	130	128	125	130
86	86	80	78	84	86	84	88	84	116	112	94	90	98	100	114
83	84	88	90	92	86	85	90	84	134	130	118	122	120	122	114
86	80	85	88	83	80	78	87	80	118	114	112	116	115	122	128
80	78	75	74	72	70	74	70	72	122	118	110	114	112	120	118
74	70	78	70	68	74	68	72	72	128	124	122	125	122	130	132
66	76	78	80	70	84	80	78	76	135	132	128	130	127	125	134
83	83	80	79	77	80	76	79	81	120	116	98	94	102	117	116
84	85	80	88	82	85	83	80	86	126	124	116	120	125	118	114
75	77	79	83	80	78	81	82	80	137	134	126	130	127	125	128
84	66	70	72	66	68	70	72	68	128	124	116	120	122	125	132
74	70	72	78	80	72	74	73	70	132	128	118	121	115	114	126
80	74	77	69	70	72	75	69	71	135	132	124	127	132	122	127
84	90	86	88	84	86	86	86	88	118	114	110	114	116	122	126
85	77	74	79	85	84	86	78	74	127	124	122	125	120	122	118
84	82	85	90	87	82	77	81	77	132	128	97	94	100	112	116
82	70	79	81	88	80	78	74	79	130	126	122	125	122	126	128
83	90	88	86	88	92	87	85	86	126	122	108	112	118	115	119
80	80	74	78	88	82	85	84	80	112	108	110	114	116	118	114
78	77	79	82	84	79	77	74	80	132	128	126	130	128	125	124
84	79	81	84	83	80	77	79	83	127	124	118	122	126	130	128
75	84	90	84	80	79	91	83	84	125	122	116	120	128	127	125
80	86	80	84	82	84	86	90	82	136	132	118	122	122	117	121
78	86	84	88	86	84	88	82	85	112	108	106	110	108	112	116
75	80	92	90	86	88	82	86	88	132	128	120	124	122	135	130
84	90	88	88	86	86	84	86	80	136	138	126	130	128	120	130
88	88	84	88	85	89	93	87	84	108	104	106	110	112	110	115
73	75	73	73	77	70	74	78	72	128	124	94	90	98	118	124
66	68	78	70	66	74	72	70	66	104	101	94	98	96	112	120
80	80	78	74	76	78	78	74	80	132	128	126	130	128	127	124
84	84	86	79	77	75	79	74	73	126	122	118	122	120	126	127
88	87	89	82	88	91	78	83	85	118	114	108	112	116	114	120

Hg)				Diastolic blood pressure (mm Hg)											
75	90	105	120	0	5	10	15	30	45	60	75	90	105	120	0
128	120	118	116	77	74	77	80	72	75	73	82	70	73	81	117
120	116	125	122	77	74	68	71	73	75	70	69	71	76	71	120
118	112	110	116	85	82	80	82	78	73	70	82	77	79	80	116
124	128	126	120	71	68	65	68	70	72	66	64	68	67	69	116
132	126	125	127	66	63	65	68	70	71	65	73	64	63	67	128
134	128	126	130	85	82	78	81	80	78	77	74	72	75	77	131
136	132	124	122	74	71	67	70	72	69	67	70	66	69	71	121
136	139	130	132	74	71	76	79	72	68	75	70	77	80	73	133
112	110	112	114	82	80	62	66	64	70	68	66	74	72	70	108
112	122	118	116	75	72	64	60	66	68	64	70	71	66	69	107
130	128	127	130	79	76	70	72	73	81	77	72	82	72	82	127
125	117	110	115	68	65	62	65	62	60	73	64	67	71	66	115
116	110	114	117	73	70	66	69	77	73	80	81	72	73	75	114
115	125	127	120	68	65	74	77	72	72	74	70	69	71	74	122
118	124	122	120	68	65	64	67	69	66	70	72	68	67	70	121
126	128	130	132	82	79	78	81	78	73	72	75	73	78	72	131
116	114	118	114	75	72	66	70	68	69	70	67	71	69	80	116
128	122	120	118	85	82	60	56	77	75	73	77	73	78	74	108
110	113	108	112	75	72	62	61	63	68	70	69	68	65	71	112
130	132	135	132	79	76	70	72	77	68	74	70	82	73	72	131
128	126	125	120	64	61	65	68	60	72	70	67	69	74	77	120
133	125	120	124	80	77	70	73	72	70	70	75	76	73	74	126
132	128	122	120	78	75	68	71	73	69	70	71	68	75	77	122
110	127	125	120	81	78	75	78	74	77	72	69	72	65	67	120
114	118	125	122	84	81	65	68	70	72	69	68	70	73	68	113
122	128	125	126	71	68	62	65	64	70	66	68	70	67	70	124
132	120	128	125	78	75	77	80	72	73	75	70	69	77	67	127
122	117	114	118	73	70	51	54	70	69	80	74	76	71	67	107
118	108	106	114	78	75	76	80	78	73	77	81	72	76	72	115
108	112	110	108	72	70	64	67	66	69	65	66	70	68	67	110
123	117	114	126	77	74	67	70	69	72	67	70	72	70	73	122
118	110	124	118	70	67	70	73	77	72	78	73	70	68	81	121
108	106	114	110	79	76	70	72	70	74	70	72	70	73	72	110
128	124	130	132	82	79	72	76	74	72	75	71	73	70	77	129
108	110	117	108	71	68	70	72	69	77	74	69	80	77	73	112
120	127	118	122	76	73	67	70	69	71	72	70	68	67	69	122
115	117	110	114	82	79	60	63	60	68	71	69	72	70	73	109
116	115	122	114	65	62	68	71	74	68	71	74	72	69	78	115
130	127	125	128	67	64	68	71	74	69	77	71	80	73	69	129
130	127	124	118	75	72	68	71	85	80	75	85	85	85	80	122
128	130	136	125	83	80	70	72	77	78	80	73	72	77	72	126
122	130	132	128	79	76	66	70	72	77	72	69	73	75	72	129
126	128	134	122	73	70	66	69	68	66	70	71	66	69	70	125
117	116	118	114	77	74	67	70	73	74	70	72	73	70	71	117
128	114	120	116	82	79	76	80	73	80	72	77	69	73	76	117

114	116	125	120	66	63	66	69	71	64	69	67	63	65	69	119
125	132	122	130	82	78	76	80	76	73	75	71	70	77	75	130
120	116	120	116	73	70	66	69	67	70	66	69	67	70	71	117
123	132	126	124	78	75	74	77	72	70	73	74	72	70	74	124
110	114	110	112	62	65	62	65	69	62	71	69	63	70	68	111
132	125	127	122	70	67	76	80	72	80	68	66	72	68	66	124
120	116	125	122	75	72	62	60	62	70	67	65	69	70	65	115
125	122	130	127	85	82	87	90	85	78	80	88	82	80	88	128
118	110	112	108	66	63	60	62	60	68	64	65	72	70	65	109
115	122	116	114	68	65	60	64	72	63	70	72	68	62	68	116
134	128	126	130	82	80	74	77	74	79	80	73	76	72	77	125
124	114	118	122	78	75	76	80	82	77	75	74	76	79	72	120
112	110	122	114	73	70	66	70	68	70	67	72	69	66	70	115
128	125	133	128	75	72	76	80	85	70	68	72	66	70	68	129
112	122	118	116	81	78	60	62	64	70	69	72	70	72	73	107
118	116	122	119	83	80	70	74	77	73	76	73	78	74	72	120
120	125	130	120	85	82	87	90	85	85	80	88	80	80	80	119
115	114	118	113	77	74	77	80	85	80	75	85	85	85	80	113
122	126	130	122	68	65	63	66	70	72	75	68	70	73	70	123
128	132	130	128	85	82	87	90	85	92	80	88	84	80	82	129
128	122	111	113	82	80	63	66	69	71	73	77	80	75	73	107
122	120	125	126	70	67	77	80	88	80	75	85	82	78	80	124
132	130	127	133	86	83	87	90	85	85	95	88	80	80	80	132
125	120	128	120	64	60	65	68	62	70	72	70	72	66	64	120
110	117	108	112	75	72	70	72	69	67	65	69	70	68	72	115
126	125	119	124	73	70	64	67	69	66	70	68	64	67	69	125
120	127	115	118	75	72	76	80	85	88	75	83	79	77	83	117
123	129	122	120	81	78	70	74	76	70	72	77	72	74	70	122
114	114	109	122	77	74	63	60	63	69	75	68	70	69	71	113
120	122	128	132	86	83	84	87	85	84	87	88	80	82	82	130
122	128	125	117	72	70	64	67	65	68	63	66	69	67	68	115
108	112	110	108	74	70	67	70	69	67	69	65	68	70	67	110
128	126	130	128	72	70	70	72	77	73	75	72	68	67	75	129
128	123	120	118	85	82	75	78	85	77	80	82	80	72	74	119
124	120	122	130	83	80	77	80	77	70	71	75	79	82	78	127
123	117	119	126	79	78	71	74	73	75	77	72	75	70	73	125
108	106	114	110	71	68	65	68	69	72	75	70	73	69	67	110
128	124	130	132	84	80	77	80	78	75	77	73	76	74	77	129
127	128	130	125	82	80	74	77	80	82	80	78	67	71	77	127
112	108	112	110	68	65	63	60	66	62	64	69	72	68	70	110
120	127	118	122	85	82	62	65	69	71	73	76	73	78	80	111
115	117	110	114	75	72	66	69	72	69	70	72	70	73	69	109
122	130	132	128	70	66	64	67	66	69	65	71	74	70	67	129
118	114	125	120	75	72	70	72	72	78	68	70	71	66	68	121
118	126	122	120	78	75	87	90	82	78	80	75	72	74	76	117

Mean arterial pressure (mm Hg)										SpO2 (%)					
5	10	15	30	45	60	75	90	105	120	0	5	10	15	30	45
114	90	94	95	91	93	89	94	85	74	99	99	99	99	99	99
116	86	89	88	90	90	85	88	88	76	99	99	99	99	99	98
112	90	94	91	93	88	84	91	90	81	99	98	98	98	98	99
112	80	83	85	87	89	87	85	85	68	99	99	99	98	99	99
124	84	87	89	89	91	85	90	85	64	99	99	99	97	99	99
128	97	100	97	95	97	94	91	91	78	99	99	99	99	99	99
118	90	90	89	88	91	89	88	85	71	98	99	99	99	99	99
130	90	93	98	91	91	96	90	95	78	99	99	99	99	99	99
105	87	89	79	83	84	82	81	87	75	99	99	99	99	99	99
104	80	83	73	82	83	83	86	86	69	99	99	99	99	99	99
124	90	93	90	89	97	94	90	98	74	99	99	99	99	99	99
112	81	84	83	84	82	88	79	83	70	99	99	99	99	99	99
110	82	85	90	91	87	90	92	87	73	98	99	99	99	99	99
118	85	88	95	87	86	91	89	86	70	99	99	99	98	99	99
118	82	85	84	84	83	88	89	85	67	99	99	99	99	99	99
128	96	99	96	95	91	91	93	93	79	99	99	99	99	99	99
112	86	89	87	85	85	85	84	85	71	99	99	99	99	99	99
105	64	67	76	93	93	89	91	88	80	99	99	99	99	99	99
108	86	88	79	81	82	84	82	83	68	99	99	99	99	99	99
128	96	99	90	93	89	93	92	99	75	98	99	99	99	99	99
117	78	82	84	78	91	89	86	86	71	99	99	99	99	99	99
123	94	97	91	90	91	88	90	92	75	99	99	99	99	99	99
118	90	92	88	89	90	89	88	85	76	99	99	99	99	99	99
116	92	95	95	88	88	90	88	88	70	99	98	98	98	99	99
110	86	89	83	85	86	85	87	87	77	99	99	99	99	99	99
121	84	87	82	85	87	87	87	89	68	99	99	99	99	99	99
124	92	96	96	90	93	90	89	88	77	99	99	99	99	99	99
104	63	66	75	89	87	92	87	90	72	98	99	99	99	99	99
112	90	91	92	89	88	87	89	86	77	99	99	99	99	99	99
108	84	87	84	82	82	81	81	83	69	99	99	99	99	99	99
118	90	92	86	83	89	84	85	90	72	99	99	99	99	99	99
118	84	87	89	90	87	89	90	86	69	99	99	99	99	99	99
107	86	89	85	85	85	82	86	83	75	99	99	99	99	99	98
126	92	95	96	93	91	91	91	93	74	99	99	99	98	99	99
108	85	88	86	83	87	86	85	89	75	99	99	99	99	99	99
118	88	91	86	87	87	90	86	86	70	99	99	99	99	99	99
106	84	87	79	80	84	86	83	86	74	99	99	99	99	99	99
112	78	81	88	86	84	86	90	86	68	99	99	99	99	99	99
126	87	90	91	94	89	94	89	96	71	99	99	99	99	99	99
118	90	92	90	98	97	92	98	96	82	99	99	99	99	99	99
122	98	101	90	91	95	97	94	90	79	99	99	99	99	99	99
126	92	95	89	89	92	91	90	91	76	99	99	99	99	99	99
122	93	91	90	87	86	89	92	85	70	99	99	99	99	99	99
114	90	93	87	91	88	85	87	87	72	99	98	98	98	99	99
114	92	95	92	90	96	86	91	85	76	99	99	99	99	99	99

116	81	84	86	87	81	85	86	82	65	99	99	99	99	99	99
127	94	97	95	94	90	94	88	90	79	99	99	99	99	99	99
114	84	87	85	85	87	83	86	83	71	99	99	99	99	99	99
121	90	94	92	91	88	93	91	89	73	98	99	99	99	99	99
108	74	77	82	85	78	85	83	79	67	99	99	99	99	99	99
120	85	88	94	88	97	87	86	89	69	99	99	99	99	99	99
112	82	85	81	83	87	83	85	87	72	99	99	99	99	99	99
124	98	101	103	100	94	94	102	97	82	99	99	99	99	99	99
106	80	82	78	79	85	79	81	84	69	99	99	99	98	99	99
112	82	86	83	87	80	87	87	83	64	99	99	99	99	99	99
122	90	94	92	91	97	96	91	94	75	99	99	99	99	99	99
116	88	92	93	95	93	88	89	91	79	99	99	99	99	99	99
112	84	87	86	86	84	81	89	84	68	99	99	99	99	99	99
126	90	93	95	100	89	87	92	87	72	99	99	99	99	99	99
104	84	87	75	81	84	87	87	85	75	99	99	99	99	99	99
116	92	95	90	89	88	89	89	92	77	99	99	99	99	99	99
116	92	95	101	99	97	95	102	93	82	99	99	99	99	99	99
110	86	89	93	96	92	88	96	94	82	99	99	99	99	99	99
120	83	86	87	91	89	92	89	87	71	99	98	98	98	99	98
126	96	99	102	101	104	97	102	99	82	99	99	99	99	99	99
104	86	89	83	85	90	89	88	91	77	99	99	99	99	99	99
121	85	88	93	97	94	90	98	97	75	99	99	99	99	99	99
129	97	100	102	99	101	107	101	98	82	99	99	99	99	99	99
117	80	83	87	85	88	88	89	88	65	99	99	99	99	99	99
112	85	88	86	88	81	82	82	84	70	99	99	99	99	99	99
122	90	93	85	88	86	88	85	84	69	99	99	99	99	99	99
114	86	89	94	99	99	92	94	92	76	98	99	99	99	99	99
119	90	94	90	90	88	91	92	88	76	99	99	99	99	99	99
110	82	85	77	81	84	88	82	87	72	99	99	99	98	99	99
127	95	98	100	99	96	99	101	97	83	99	99	99	99	99	99
112	84	87	83	83	86	85	86	85	69	99	99	99	99	99	99
107	85	88	86	84	81	83	80	81	71	99	99	99	99	99	99
126	88	91	90	93	91	92	91	88	69	99	99	99	99	99	99
116	96	99	95	99	94	94	95	93	76	99	99	99	99	99	99
124	95	98	96	93	88	87	91	96	82	99	99	99	99	99	99
122	90	93	88	89	91	90	88	92	73	99	99	99	99	99	99
107	80	83	83	85	84	85	85	85	70	99	99	99	99	99	99
126	94	97	98	95	93	93	92	95	77	99	98	99	99	99	98
124	94	97	91	97	97	96	95	86	75	99	99	99	98	99	99
107	80	83	77	82	79	79	83	85	68	99	98	98	99	99	99
108	86	89	83	87	87	91	90	89	80	99	98	99	99	99	99
106	78	82	83	88	84	86	85	85	74	98	98	99	99	99	99
126	86	89	87	85	87	87	91	92	70	99	99	99	99	99	99
118	87	90	90	90	91	83	88	87	69	99	99	99	99	99	99
114	88	91	98	95	91	95	91	88	75	99	99	99	99	99	99

					Temperature (degree C)									
60	75	90	105	120	0	5	10	15	30	45	60	75	90	105
99	99	99	99	99	36.4	36.3	35.8	35.8	35.6	36	36.2	36	36.2	36.5
99	99	99	99	99	36.5	36.1	36.2	36	36.2	36	36.4	36.5	36.6	36.1
99	99	99	99	99	36	36.2	36.1	35.9	36	36.2	35.8	36.3	36.5	36.2
99	99	99	98	99	36.2	36	36.2	35.8	36	36.4	36.2	36.1	36.3	36
99	99	99	99	99	36.1	36	36.1	35.8	36	36.1	36.6	35.8	36	36.2
99	99	99	99	99	36.3	35.8	36.2	36.1	36.4	36.2	35.8	36.3	36.6	36.2
99	99	99	99	99	36	36.2	36	35.9	35.8	36.5	36.4	36.2	35.9	36.5
99	99	99	99	99	36.4	36.1	36	36	35.7	36.5	36.4	36.8	36.6	36.4
99	99	99	99	99	36.5	36.2	36.1	36	36.3	35.9	35.8	36.2	36	36.9
99	99	99	99	99	36.2	36.1	36.1	36	35.7	36	36.2	35.8	36.2	36
99	99	99	99	99	36.4	36.2	36.4	35.8	35.6	36	36.2	36	36.2	36.5
99	99	99	99	99	36.5	36	36.2	36	36.2	36	36.4	36.5	36.6	36.1
99	99	98	99	99	36	36	36.3	35.9	36	36.2	35.8	36.3	36.5	36.2
99	99	99	99	99	36.2	36.1	36.3	35.8	36	36.4	36.2	36.1	36.3	36
99	99	99	99	99	36.1	36.1	36.2	35.8	36	36.1	36.6	35.8	36	36.2
99	99	99	99	99	36.3	36.4	36.4	36.1	36.4	36.2	35.8	36.3	36.6	36.2
99	99	99	99	99	36	36.2	36.2	35.9	35.8	36.5	36.4	36.2	35.9	36.5
99	99	99	99	99	36.4	36.3	36.4	36	35.7	36.5	36.4	36.8	36.6	36.4
99	99	99	98	99	36.5	36.3	36.4	36	36.3	35.9	35.8	36.2	36	36.9
99	99	99	99	99	36.2	36.2	36.2	36	35.7	36	36.2	35.8	36.2	36
99	99	99	99	99	36	36.4	36.2	36.5	36.3	35.9	36	36	36.1	36.2
99	99	99	99	99	36.2	36.3	36.5	35.9	36.4	36.4	36.2	36.2	36.1	36
99	99	99	99	99	36.5	36.1	36.2	36.1	36.1	36.1	36.2	36.3	36.4	36.2
99	99	99	99	99	35.8	36.2	35.8	36.1	36.5	35.9	36.3	36	36.2	36.2
99	99	99	99	99	36.3	36	36.2	36.2	36.3	36.3	35.9	36.4	36.5	36.4
99	99	99	99	99	36.1	36	36.1	36.3	36	36	36.1	36	36.4	36.3
99	99	99	99	99	36.6	35.8	36.2	36	35.9	36.1	36.2	36.5	36.5	36.4
99	99	99	99	99	36.4	36.2	36.1	36.1	36.2	35.9	36.4	35.9	36	36.5
99	99	99	99	99	36	36.1	36.2	35.9	36	36.5	36.2	36.3	36.2	36.1
99	99	99	99	99	36.8	36.2	36	36.6	35.8	36.1	36.3	36.5	36.6	36.5
99	99	99	99	99	36.4	36.1	36	35.8	35.6	36	36.2	36	36.2	36.5
99	99	99	99	99	36.5	36.2	36.1	36	36.2	36	36.4	36.5	36.6	36.1
99	99	99	99	99	36	36	36.1	35.9	36	36.2	35.8	36.3	36.5	36.2
99	99	99	99	99	36.2	36	36.4	35.8	36	36.4	36.2	36.1	36.3	36
99	99	99	99	99	36.1	36.1	36.2	35.8	36	36.1	36.6	35.8	36	36.2
99	99	99	99	99	36.3	36.1	36.3	36.1	36.4	36.2	35.8	36.3	36.6	36.2
99	99	99	99	99	36	36.4	36.3	35.9	35.8	36.5	36.4	36.2	35.9	36.5
99	99	99	99	99	36.4	36.2	36.2	36	35.7	36.5	36.4	36.8	36.6	36.4
99	99	99	99	99	36.5	36.3	36.4	36	36.3	35.9	35.8	36.2	36	36.9
99	99	98	98	99	36.2	36.3	36.2	36	35.7	36	36.2	35.8	36.2	36
99	99	99	99	99	36	36.2	36.4	36.5	36.3	35.9	36	36	36.1	36.2
99	99	99	99	99	36.2	36.4	36.4	35.9	36.4	36.4	36.2	36.2	36.1	36
99	99	99	99	99	36.5	36.3	36.2	36.1	36.1	36.1	36.2	36.3	36.4	36.2
99	99	99	99	99	35.8	36.1	36.2	36.1	36.5	35.9	36.3	36	36.2	36.2
99	99	99	99	99	36.3	36.2	36.5	36.2	36.3	36.3	35.9	36.4	36.5	36.4

99	99	99	99	99	36.1	36	36.5	36.3	36	36	36.1	36	36.4	36.3
99	99	99	99	99	36.6	36	36.1	36	35.9	36.1	36.2	36.5	36.5	36.4
99	99	99	99	99	36.4	35.8	36.2	36.1	36.2	35.9	36.4	35.9	36	36.5
99	99	99	99	99	36	36.2	35.8	35.9	36	36.5	36.2	36.3	36.2	36.1
99	99	99	99	99	36.8	36.1	36.2	36.6	35.8	36.1	36.3	36.5	36.6	36.5
99	99	99	99	99	36.4	36.2	36.1	35.8	35.6	36	36.2	36	36.2	36.5
99	99	99	99	99	36.5	36.1	36.2	36	36.2	36	36.4	36.5	36.6	36.1
99	99	99	99	99	36	36.2	36.1	35.9	36	36.2	35.8	36.3	36.5	36.2
99	99	99	99	99	36.2	36	36.2	35.8	36	36.4	36.2	36.1	36.3	36
99	99	99	99	99	36.1	36	36	35.8	36	36.1	36.6	35.8	36	36.2
99	99	99	99	99	36.3	36.1	36	36.1	36.4	36.2	35.8	36.3	36.6	36.2
99	99	99	99	99	36	36.1	36.1	35.9	35.8	36.5	36.4	36.2	35.9	36.5
99	99	99	99	99	36.4	36.4	36.1	36	35.7	36.5	36.4	36.8	36.6	36.4
99	99	99	99	99	36.5	36.2	36.4	36	36.3	35.9	35.8	36.2	36	36.9
99	99	98	99	99	36.2	36.3	36.2	36	35.7	36	36.2	35.8	36.2	36
99	99	99	99	99	36	36.3	36.3	36.5	36.3	35.9	36	36	36.1	36.2
99	99	99	99	99	36.2	36.2	36.3	35.9	36.4	36.4	36.2	36.2	36.1	36
99	99	99	99	99	36.5	36.4	36.2	36.1	36.1	36.1	36.2	36.3	36.4	36.2
99	99	99	99	99	35.8	36.3	36.4	36.1	36.5	35.9	36.3	36	36.2	36.2
99	99	99	99	99	36.3	36.1	36.2	36.2	36.3	36.3	35.9	36.4	36.5	36.4
99	99	99	98	99	36.1	36.2	36.4	36.3	36	36	36.1	36	36.4	36.3
99	99	99	99	99	36.6	36	36.4	36	35.9	36.1	36.2	36.5	36.5	36.4
99	99	99	99	99	36.4	36	36.2	36.1	36.2	35.9	36.4	35.9	36	36.5
99	99	99	99	99	36	35.8	36.2	35.9	36	36.5	36.2	36.3	36.2	36.1
99	99	99	99	99	36.8	36.2	36.5	36.6	35.8	36.1	36.3	36.5	36.6	36.5
99	99	99	99	99	36.4	36.1	36	35.8	35.6	36	36.2	36	36.2	36.5
99	99	99	99	99	36.5	36.2	36	36	36.2	36	36.4	36.5	36.6	36.1
99	99	99	99	99	36	36.1	36.1	35.9	36	36.2	35.8	36.3	36.5	36.2
99	99	99	99	99	36.2	36.2	36.1	35.8	36	36.4	36.2	36.1	36.3	36
99	99	99	99	99	36.1	36	36.4	35.8	36	36.1	36.6	35.8	36	36.2
99	99	99	99	99	36.3	36	36.2	36.1	36.4	36.2	35.8	36.3	36.6	36.2
99	99	99	99	99	36	36.1	36.3	35.9	35.8	36.5	36.4	36.2	35.9	36.5
99	99	98	99	99	36.4	36.1	36.3	36	35.7	36.5	36.4	36.8	36.6	36.4
99	99	99	99	99	36.5	36.4	36.2	36	36.3	35.9	35.8	36.2	36	36.9
99	99	99	99	99	36.2	36.2	36.4	36	35.7	36	36.2	35.8	36.2	36
99	99	99	99	99	36	36.3	36.2	36.5	36.3	35.9	36	36	36.1	36.2
99	99	99	99	99	36.2	36.3	36.4	35.9	36.4	36.4	36.2	36.2	36.1	36
99	99	99	98	99	36.5	36.2	36.4	36.1	36.1	36.1	36.2	36.3	36.4	36.2
99	99	99	99	99	35.8	36.4	36.2	36.1	36.5	35.9	36.3	36	36.2	36.2
99	99	99	99	99	36.3	36.2	36.2	36.2	36.3	36.3	35.9	36.4	36.5	36.4
99	99	99	99	99	36.1	36.4	36.2	36.3	36	36	36.1	36	36.4	36.3
99	99	99	99	99	36.6	36.4	36.4	36	35.9	36.1	36.2	36.5	36.5	36.4
99	99	99	99	99	36.4	36.2	36	36.1	36.2	35.9	36.4	35.9	36	36.5
99	99	98	99	99	36	36.2	36	35.9	36	36.5	36.2	36.3	36.2	36.1
99	99	99	99	99	36.8	36.5	36.2	36.6	35.8	36.1	36.3	36.5	36.6	36.5

120	Brady	Hypoten	Respiration
36.5	N	N	N
36.4	N	N	N
36.4	Y	N	N
36.4	N	N	N
36.5	N	N	N
36.5	N	N	N
36.8	N	N	N
36.6	N	N	N
36.5	N	N	N
35.9	N	N	N
36.5	N	N	N
36.4	N	N	N
36.4	N	N	N
36.4	N	N	N
36.5	N	N	N
36.5	N	N	N
36.8	N	N	N
36.6	Y	Y	N
36.5	N	N	N
35.9	N	N	N
36.2	N	N	N
36.6	N	N	N
36.4	N	N	N
36	N	N	N
36.3	N	N	N
36.5	N	N	N
36.4	N	N	N
36.2	Y	Y	N
35.9	N	N	N
36.4	N	N	N
36.5	N	N	N
36.4	N	N	N
36.4	N	N	N
36.4	N	N	N
36.5	N	N	N
36.5	N	N	N
36.8	N	N	N
36.6	N	N	N
36.5	N	N	N
35.9	N	N	N
36.2	N	N	N
36.6	N	N	N
36.4	N	N	N
36	N	N	N
36.3	N	N	N

36.5	N	N	N
36.4	N	N	N
36.2	N	N	N
35.9	N	N	N
36.4	N	N	N
36.5	N	N	N
36.4	N	N	N
36.4	N	N	N
36.4	N	N	N
36.5	N	N	N
36.5	N	N	N
36.8	N	N	N
36.6	N	N	N
36.5	N	N	N
35.9	N	N	N
36.2	N	N	N
36.6	N	N	N
36.4	N	N	N
36	N	N	N
36.3	N	N	N
36.5	N	N	N
36.4	N	N	N
36.2	N	N	N
35.9	N	N	N
36.4	N	N	N
36.5	N	N	N
36.4	N	N	N
36.4	N	N	N
36.4	N	N	N
36.5	N	N	N
36.5	N	N	N
36.8	N	N	N
36.6	N	N	N
36.5	N	N	N
35.9	N	N	N
36.2	N	N	N
36.6	N	N	N
36.4	N	N	N
36	N	N	N
36.3	N	N	N
36.5	N	N	N
36.4	N	N	N
36.2	N	N	N
35.9	N	N	N
36.4	N	N	N

Plagiarism report